American Journal of Obstetrics and Gynecology

VOL. 38 AUGUST, 1939 No. 2

Original Communications

THE TREATMENT OF HEMOLYTIC STREPTOCOCCAL INFECTIONS DURING PREGNANCY AND THE PUERPERIUM, WITH SULFANILAMIDE AND IMMUNOTRANSFUSION

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INTRODUCTION

THE use of sulfanilamide in the treatment of puerperal infections, especially those caused by the hemolytic streptococcus, is now established on a sound clinical basis. In a series of 106 cases reported by Colebrook and Purdie,[1] the total case fatality rate of sulfanilamide treated cases as compared with the total case fatality rate in puerperal sepsis prior to the use of sulfanilamide has been decreased from an average of 22 to 8 per cent. That this decrease is due to the sulfanilamide and not to a diminution in the virulence of the organism is shown by the fact that the incidence of bacteriemia has remained about the same since the advent of the drug while the fatality rate in treated bacteriemic cases as compared with the fatality rate in untreated bacteriemic cases has been decreased from an average of 71 to 27 per cent.[1] Thus, as a result of this new therapeutic agent puerperal sepsis is no longer the grave obstetric problem it once was. To assume that it is no longer any problem or to rely wholly on sulfanilamide without regard to the bacteriologic aspects of each case would be dangerous because not all strains of hemolytic streptococci are equally susceptible to the action of sulfanilamide. The intelligent management of puerperal infections and the rational use of sulfanilamide in such infections should, therefore, be based to some extent upon a knowledge of the bacteriologic status of the infecting organism and the immunologic status of the patient. The purpose of the present paper is to outline a method of treatment of

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puerperal streptococcal infections in the light of the most recent experimental studies on the hemolytic streptococcus. The laboratory techniques discussed in the paper will be given in detail in the appendix.

THE CLASSIFICATION OF THE HEMOLYTIC STREPTOCOCCI

Until comparatively recently, the problem of the classification of the streptococci has been a confused one. Much of this confusion arose as a result of the innumerable bases of classification adopted by different observers. One method of differentiation was based on fermentative reactions, another, on the type of disease from which the strains were isolated, another, on the kind of hemolysis produced by different strains and so on. Schottmüller[2] in 1903 first differentiated streptococci on the basis of hemolysis, but it was not until the work of Brown[3] and of Brown and Smith[4] that this system of differentiation was developed in detail. Brown distinguished between strains of streptococci which produced no hemolysis in blood agar plates* and those which produced either partial or complete hemolysis on the same media. Those strains producing partial hemolysis, such as the pneumococcus and the *Streptococcus viridans*, he designated as alpha, those producing complete hemolysis as beta, and those giving rise to no hemolysis as gamma. The organisms commonly known as hemolytic streptococci all belong in the beta category and in this paper discussion will be limited to this group.

Dissociation.—Within the group of beta hemolytic streptococci, the same confusion in classification has prevailed as among the streptococci in general. In the matter of variation or dissociation, for example, very little agreement has been reached until recently. It is not within the scope of this paper to discuss bacterial dissociation but a brief explanation of its significance may be of value to the reader. In 1921, Arkwright[5] studying the colon-typhoid-dysentery group of bacteria found in old cultures two types of colonies. The one he designated "smooth" because of its glossy, shining surface and even edges. The other he termed "rough" because of its dull, uneven surface and irregular edges. It was soon found that smooth strains were more virulent for man and animal than rough strains and that almost all bacteria had the capacity to produce smooth or rough colonies under suitable conditions. Later, a third variant called "mucoid" because of its watery, glistening, mucoid appearance was described. At the present time the three variants, mucoid, smooth, and rough have been described for many bacteria, including the pneumococcus and the streptococcus. The significance of the phenomenon of dissociation for the clinician lies in the fact that there is a definite correlation between variation and virulence. In general, mucoid strains are associated with severe infections in man, smooth strains with milder human infections, while rough strains are rarely if ever responsible for human disease.

In the case of the hemolytic streptococcus Dawson, Hobby and Olmstead[6] have shown that this organism, like the pneumococcus, can exist in three dissociative phases i.e., mucoid, smooth, and rough. In the first phase the colonies are mucoid, the bacteria are encapsulated and the strains producing these forms are usually virulent and possess type-specificity.† In the second phase, the colonies are smooth, the bacteria are not encapsulated, the strains possess little or no virulence, and they may or may not possess type-specificity. In the third phase, the colonies are rough, the bacteria are not encapsulated, the strains are completely avirulent and are lacking in type-specificity.

*It cannot be emphasized too strongly that the type of hemolysis can be distinguished with certainty only in deep pour plates and in media containing no dextrose since dextrose inhibits hemolysis.

†Depending upon the presence of the "M" substance of Lancefield.

Grouping and Typing.—With regard to the problem of the serologic grouping and typing of hemolytic streptococci innumerable investigations have been carried out. To Lancefield[7] and to Griffith,[8] however, belong the credit for the most valuable contributions along these lines. Griffith by the technique of slide-agglutination demonstrated that hemolytic streptococci could be differentiated into serologically distinct types. Lancefield using precipitative methods found that these organisms elaborated a type-specific, proteinlike material which she designated the "M" substance, and a group specific antigen, carbohydrate in nature which she named the "C" substance. On the basis of the group antigen, Lancefield found that hemolytic streptococci could be classified into groups according to the source from which they were isolated. All human, pathogenic strains with rare exceptions fell into one group (Group A); strains producing mastitis in cattle into another (Group B); strains from milk and cheese into still other groups, etc. At the present time at least nine* different groups have been demonstrated by the Lancefield technique. The latest work of Evans and Verder[9] indicates that the Lancefield groups can also be differentiated with a high degree of accuracy by fermentative reactions and sensitivity to bacteriophage B. So far as human pathogenicity goes only Group A strains are of prime importance, although in some instances Group B, C, D, and G have been responsible for human infections. Group D strains have frequently been isolated from the vagina of normal individuals and occasionally have caused mild urinary tract infections.

Both Griffith and Lancefield by the methods already mentioned have subdivided Group A strains into some 25 serologic types. From an immunologic and epidemiologic point of view their work has been extremely valuable but so far has not been of much aid therapeutically because of the practical difficulties inherent in making protective antistreptococcal sera against such a diversity of types. In fact, it has always been extremely difficult to produce even a single type-specific serum with the hemolytic streptococcus. The only vaccines which have been found to stimulate the production of the protective antisera have been those which contained some living organisms. The reason that living organisms are necessary involves a consideration of the antigenic structure of the hemolytic streptococcus in relation to virulence and immunity.

Virulence and Immunity.—In 1897, Bordet,[10] studying the hemolytic streptococci, noticed that when guinea pigs were injected intraperitoneally with this organism, most of the cocci were rapidly phagocytosed. The few that remained unengulfed soon developed capsules, continued to resist phagocytosis and ultimately brought about the death of the animal. The development of a capsule appeared to be a mechanism whereby the organism protected itself against phagocytosis and eventual destruction. The work of Todd,[11] Hare,[12] and of Seastone,[13] at a much later date confirmed Bordet's observations. Working independently, each of these investigators correlated resistance to phagocytosis with encapsulation of the organism but pointed out that only in very young cultures or in the animal body were capsules present on the organism. In older cultures (eight to twenty-four hours) the capsules disappeared only to reappear upon transference of some of the culture to fresh medium or injection of some of it into an experimental animal. More light was shed on the mode of destruction of hemolytic streptococci when Ward and Lyons[14] showed that sensitization of virulent streptococci to phagocytosis was brought about by a type-specific antibody or opsonin. This antibody or opsonin against a particular type of organism was found to be present in the blood of certain normal individuals and to a much greater extent in the blood of patients who had recovered from a streptococcal infection caused by the same type. This observation led to the development of a technique for the selection of immune donors for transfusions in streptococcal infections (Lyon[15]). The attempts to produce actively opsonic antisera in rabbits were attended with great difficulty and satisfactory titers were only obtained by repeated injections of living organisms.

*Sera against Groups A, B, and C have been prepared by Lederle Laboratories, New York, and are now available for diagnostic purposes.

At the present time, owing to the impracticability of producing streptococcal *antibacterial* sera commercially, there is no such serum for clinical use on the market. When specific antibody is needed in the treatment of septic streptococcal infections the only source available is the blood of an immune donor.

Toxin Production.—The hemolytic streptococcus elaborates at least 5 filterable exotoxins. These are: (1) hemolysin, (2) leucocidin, (3) erythrogenic toxin, (4) fibrinolysin, and (5) the "spreading factor" of Duran-Reynals.[16] The hemolysin or streptolysin lyses red blood corpuscles in vitro and exerts a toxic effect in the animal body. The nature of the leucocidin which is capable of destroying leucocytes in vitro is not definitely known. Whether or not it is identical with the streptolysin remains in doubt although the bulk of the evidence would suggest that it is a different substance. Fibrinolysin, as the name implies, possesses the ability to liquify human plasma or fibrin clot. It is elaborated by almost all Group A strains. The filtrates of invasive streptococci contain another toxic substance called the "spreading factor." As yet very little is known about this substance beyond the fact that it increases the permeability of rabbits' skin to suspensions of India ink or to bacterial cells. Menkin,[17] in his studies on inflammatory fixation, has shown that staphylococci tend to be fixed very rapidly in the tissues after subcutaneous injection, whereas streptococci under the same conditions fail to promote the formation of an inflammatory barrier for a much longer period of time. It is highly probable that the spreading factor is involved in this delayed fixation.

The importance of the erythrogenic toxin, which is responsible for the rash in scarlet fever, lies in its ability to produce a potent antitoxin in the animal body. Hooker and Follensby[18] and Hooker[19] have identified two toxins, A and B toxins, in erythrogenic toxin. The A toxin which is identical with the Dick toxin is of greater importance than the B toxin because it is elaborated by almost 90 per cent of the toxin-producing strains. Erythrogenic toxin is neither type-specific nor disease-specific. There is no such thing as scarlatinal erythrogenic toxin as differentiated from the erythrogenic toxin of erysipelas. In the production of commercial streptococcal antitoxin the strain most widely used is Dochez N. Y. 5. Since this strain elaborates both A and B toxins, the antitoxin produced by it will neutralize both toxins. Commercial streptococcal (scarlatinal) antitoxin is, therefore, of value in treating the *toxic* manifestations of any streptococcal infection, regardless of the disease entity.

THE MECHANISM OF INFECTION IN HEMOLYTIC STREPTOCOCCAL DISEASES

In the production of disease by any micro-organism two factors are involved, namely, the virulence of the organism and the resistance of the host. The virulence of the hemolytic streptococcus is determined by its ability to invade the host and multiply in the tissues and by its capacity to produce toxins within the body. Invasiveness and toxicity are separate attributes of this organism. Some strains are both highly invasive and toxic but many strains are characterized by a predominance of one or the other. The clinical picture of streptococcal disease varies depending upon which element, the septic (invasive) or the toxic, predominates.

The resistance of the host to invasion by the hemolytic streptococcus depends upon the ability of the host to destroy the organism and to neutralize the toxins produced by it. The destruction of gram-positive cocci is accomplished by the process of phagocytosis and intracellular digestion. In the case of *virulent* streptococci, as Ward and Lyons[14] have shown, phagocytosis by human leucocytes depends upon the sensitizing action of specific antibacterial antibody. The toxic products of the organisms are not influenced by antibacterial antibody and require antitoxin for their neutralization.

The mechanism of infection and recovery in streptococcal disease is determined by the factors mentioned above. In local infections, with organisms of low virulence, for example, recovery takes place through fixation of the infection at the local site without the development of circulating antibodies. In local plus invasive infections with highly virulent organisms (with or without bacteriemia), recovery occurs by local fixation plus the development of immune bodies. The practical application of these general principles to puerperal streptococcal infections will be taken up in a later section.

THE ROLE OF HEMOLYTIC STREPTOCOCCI IN PUERPERAL INFECTIONS

Weinstein[20] in investigating the bacterial flora of the vagina of women during normal pregnancy found the incidence of beta hemolytic streptococci to be approximately 4 per cent (17 out of 375 patients). No attempt was made to classify these strains serologically but the fact that none of these patients developed any complications during or following delivery suggests that they were not Group A strains. The earlier studies of Smith,[21] Paine,[22] Colebrook,[23] Hare and Colebrook,[24] Hare,[25] and Lancefield and Hare[26] brought out the fact that *virulent* hemolytic streptococci are rarely present in the vagina of normal parturient women. Lancefield and Hare for example, isolated only 13 strains of beta hemolytic streptococci out of a series of 855 women examined (vaginal culture) before delivery. Of these 13, only 2 strains were Group A strains and only one of the two resulted in puerperal sepsis. Thus the incidence of Group A strains in the human vagina before delivery is only approximately 0.25 per cent. In patients with severe puerperal infections, on the other hand, almost 100 per cent of the strains isolated fall into Group A (44 out of 45 in the series of Lancefield and Hare). All of these studies indicate that in puerperal sepsis infection occurs immediately ante or post partum and as a corollary that such infection is of exogenous and not endogenous origin. That the chief exogenous source is the nasopharynx of contacts was conclusively demonstrated by Colebrook.[27] In an extensive epidemiologic study, she found that approximately 70 per cent of the strains isolated from patients with puerperal sepsis were the same type as the strains isolated from the nasopharynx of attendant contacts or of the patient herself. This work is indirectly confirmed by the fact that Group A hemolytic streptococci, as stated previously are not present normally in the vagina before or after delivery in the absence of a definite infection and that they are not present in the feces of normal pregnant women.[28]

METHOD OF TREATMENT OF THE STREPTOCOCCAL INFECTIONS OF PREGNANCY AND THE PUERPERIUM

The normal mechanism of recovery in the streptococcal infections of pregnancy and the puerperium is essentially the same as the mechanism of recovery in streptococcal diseases in general. Local infections with strains of little or no virulence tend to remain confined to the uterus by the process of inflammatory fixation. Organisms of such low invasive power do not produce an antibody response in the body nor is antibody necessary, in general, for recovery from these infections. Treatment of infected abortions caused by noninvasive streptococci should be the treatment of any local infection, i.e., drainage and removal of the focus of infection plus general supportive measures. If the infecting strain in such a case is a Group A organism, sulfanilamide should be given preoperatively (for dosage, see the following section). This procedure is recommended as a safeguard to the patient in the event that the organism

should suddenly regain its virulence. The following case report illustrates some of the above points:

The patient, a 24-year-old, gravida ii, para i, was admitted to the Boston Lying-in Hospital with a diagnosis of incomplete abortion. Three days after admission the patient's temperature rose to 99.6° F. Cervical culture revealed the presence of beta hemolytic streptococci in pure culture. The organism isolated was a Group A strain, but on subculture it was found to be in a nonvirulent phase (S R, i.e., the colonies on Dawson's media were granular and slightly irregular in outline, the cocci were not capsulated, and broth cultures were flocculent). Prontylin was given for two days (80 gr. and 40 gr., respectively) but was discontinued because of a lowering of the red count. Both clinical and serologic evidence indicated that the infecting strain possessed no invasive properties. The patient's temperature never rose above 100° F. and symptoms and physical signs were those of a mild local infection. Serologically, the patient had little or no antibody to her own organism, indicating that the infection was a purely local one with an avirulent organism. One cubic centimeter of her own blood killed only 100 organisms. In spite of continued positive cultures, therefore, a dilatation and curettage was recommended. After a slight postoperative rise the patient's temperature fell to normal, cultures became negative and she progressed rapidly to complete recovery.

In invasive streptococcal infections during pregnancy or the puerperium, highly virulent organisms rapidly invade the tissues and ultimately enter the blood stream unless the infection is controlled before bacteriemia occurs. Recovery in such cases occurs by the process of local fixation plus the development of immune bodies. In untreated cases, if the organism is highly virulent and the patient has no antibodies to that particular strain, invasion of the blood stream takes place very rapidly and death results. If, in untreated cases, the infecting strain is moderately virulent and the patient possesses some antibody to it, local fixation may hold the infection in check until sufficient antibody is developed to prevent bacteriemia or to control it if it occurs.

In the treatment of these infections the chief weapons we possess are sulfanilamide, antibacterial antibody and erythrogenic antitoxin. Although the mode of action of sulfanilamide is still not known, its bacteriostatic effect on the hemolytic streptococcus in vitro and in vivo has been demonstrated by innumerable investigators. Not all strains, however, are equally susceptible to the action of the drug, some are completely resistant (anaerobic strains especially) while others seem to require specific antibacterial antibody in addition to the sulfanilamide for their destruction. The authors, for example, in a recent paper[29] confirmed the observation of Lyons[30] that sulfanilamide and immune serum together had a greater bactericidal effect in vitro on a virulent hemolytic streptococcus than either one alone. The clinical studies of Finland, Brown and Rauh,[31] Keefer,[32] and Lyons[30] on the use of specific antibody with sulfanilamide tend to corroborate these experimental results. The value of the application of experimental observations to clinical problems is illustrated by the following case reports.

Mrs. G. Y., a 24-year-old, para ii, was admitted to the Boston Lying-in Hospital at term with a diagnosis of sinusitis. Three days post partum she developed a septic metritis. Group A, mucoid, virulent hemolytic streptococci were isolated in pure culture from the vagina, nose, and throat. Prontylin therapy was instituted (80 gr. per day). Because the patient's initial response to sulfanilamide was unsatisfactory

and because her blood contained very little antibody to the infecting strain, immunotransfusion was advised. Four immunotransfusions were given, together with 80 gr. daily doses of prontylin. Five days after the onset of the infection, the temperature reached normal and from then on the patient convalesced rapidly to complete recovery. She was discharged from the hospital nineteen days post partum.

Mrs. M. C., a 37-year-old primipara, was admitted to the Boston Lying-in Hospital at term with a diagnosis of healing pulmonary tuberculosis. Acid-fast infection had been first diagnosed three and one-half years before admission, and sanatorium care had been instituted. Following a thirty-four-hour labor, a midforceps delivery was performed, and because the placenta failed to separate, manual removal was resorted to. Six days post partum, the patient's temperature rose to 104.4° F. Physical examination of the chest suggested renewed activity of the tuberculous process at the right apex. For this reason, uterine and blood cultures were not taken until three days later. Sulfanilamide, in 100 gr. daily doses, was started at this time. On the sixth day after the first elevation of temperature, Group A, virulent hemolytic streptococci were isolated in pure culture from the uterus and the blood stream. Because of the bacteriemia, the antibody content of the patient's blood was determined. It was found that the patient possessed no demonstrable antibody to her own organism. In view of this fact, together with the fact that the patient continued to be severely ill in spite of sulfanilamide therapy, immunotransfusion was advised.

TABLE I

DAY OF DISEASE	CONDITION OF PATIENT	SULFANILAMIDE		IMMUNOTRANSFUSIONS		PHAGOCYTIC TITER OF PATIENT	NUMBER OF BACTERIA KILLED PER C.C. OF PATIENT'S BLOOD
		DOSAGE	BLOOD LEVEL	AMOUNT	PHAGOCYTIC TITER OF DONOR		
1	Onset. Temp. 104.4° F.						
2	Dyspnea, fever, prostration						
3	Condition unchanged						
4	Very septic; blood culture taken	6.6 gm.					
5	No improvement	5.3 gm.					
6	Worse. Oxygen tent. Blood culture reported positive		7.2				
7	Condition unchanged	6.6 gm.					
8	Stuporous. Blood culture taken	6.6 gm.	3.1			0- 0%-25	0
9	Better after transfusion	6.6 gm.	4.4	600 c.c.	44-24%-25*		
10	Improving. Blood culture reported negative	8.0 gm.	5.9	500 c.c.	28-24%-25	61-20%-25	20,000
11	Improving	8.0 gm.	3.9	500 c.c.	35-16%-25		
12	Temp. normal	8.0 gm.	6.4			254-56%-25	300,000
13	Temp. normal; soft diet	8.0 gm.	8.3				
14	Temp. normal; out of oxygen tent	6.6 gm.	4.1				
15	Convalescing rapidly	6.6 gm.					
16	Convalescing rapidly						
17	Convalescing rapidly						

*The first figure indicates the number of intracellular cocci counted; the second figure, the percentage of cells containing cocci; the third figure, the number of cells counted.

Three immunotransfusions were given and sulfanilamide was continued. Seventy-two hours after the first immunotransfusion, the patient's temperature reached normal and the infection subsided. The patient was discharged from the hospital twenty-six days post partum.

The chief clinical and bacteriologic findings in this last case are summarized in Table I. Attention is called to the striking response to immunotransfusion, as evidenced by the immediate rise in the phagocytic titer and the killing power of the patient's blood. Another point to be noted is that the content of antibody in the donors' sera, as indicated by their phagocytic titers, was not very great, and yet it was sufficient to produce excellent therapeutic results. This is in line with the experience of Finland and his co-workers,[31] who found that in pneumococcal meningitis small amounts of antibody were highly effective therapeutically when given with large doses of sulfanilamide.

With regard to the use of erythrogenic antitoxin in the treatment of streptococcal infections, the following points are of importance. There is no evidence that antitoxin has any effect on the organism itself and therefore cannot be expected to be of value in the treatment of septic, invasive streptococcal infections. Patients with profound toxemia and an erythematous rash such as in puerperal scarlatina may be relieved of some of the toxic symptoms by erythrogenic antitoxin. Its use, however, should be limited to these cases. In septic and invasive infections, sulfanilamide should be given in large doses.[1, 31, 32] If clinical and serologic evidence indicates that the infecting strain is resistant to sulfanilamide, or if the patient has a positive blood culture and little or no circulating antibody, immunotransfusion is indicated.

Since it has been conclusively demonstrated that the source of infection in puerperal sepsis is exogenous,[27] the necessity for flawless, aseptic technique in the delivery room is further emphasized. If, in spite of such technique, infection occurs, then the evaluation of the patient from a bacteriologic standpoint is prerequisite to rational therapy.

RECOMMENDATIONS FOR THE TREATMENT OF HEMOLYTIC STREPTOCOCCAL INFECTIONS DURING PREGNANCY AND THE PUERPERIUM

SUMMARY

I. Isolation of Organism
   A. Isolate strain in pure culture (see Appendix I).
   B. Determine probable virulence (see Appendix I and II).
   C. Group strain by rapid precipitin method of Brown[33] (see Appendix III).

II. Management of Patient
   A. During pregnancy—septic abortion.
      1. If beta hemolytic streptococcus is present in vaginal or cervical culture and patient shows signs and symptoms of a definite infection:
         (a) Isolate patient
         (b) Start sulfanilamide. Initial dose should be 0.3 gm. (5 gr.) per 10 pounds body weight. Following initial dose, give 0.6 gm. every 4 hours until a total of 6-8 grams (for an adult of average weight) have been given in the first 24 hours. Thereafter, give a daily maintenance dose of 4 gm. Determine concentration of sulfanilamide in the blood by chemical methods 24 hours after therapy is started. Do daily chemical determinations until level is maintained steadily at 8 to 12 mg. per cent. When level is more or less constant, check blood level every three or four days.

(c) If infecting strain is a Group A, virulent organism and blood culture is positive:

(1) Determine antibody content of patient's blood (see Appendix IV and V).

(2) If little or no antibody is present in patient's blood, give 300 to 400 c.c. of blood from immune donor (see Appendix IV).

(3) Determine antibody content of patient's blood 24 hours after transfusion. If phagocytic index is not significantly increased, repeat immunotransfusion until there is evidence of sufficient antibody response.

(d) If infecting strain is a Group A, virulent organism but blood culture is negative, sulfanilamide alone should be effective. If clinical response to sulfanilamide is unsatisfactory after seventy-two hours of treatment, indicating that the strain is resistant to sulfanilamide, give immunotransfusion.

2. If infecting strain is a Group A organism but is *not* virulent according to bacteriological and clinical evidence:

(a) Isolate patient.

(b) Transfuse, if red count is low.

(c) Remove focus of infection by doing dilatation and curettage. Probably advisable to give sulfanilamide over a period of twenty-four hours preoperatively. Initial dose of 0.3 gm. (5 gr.) per 10 pounds body weight, followed by 0.6 gm. every four hours until 6 or 8 gm. have been given.

(d) Immunotransfusion is not indicated unless bacteriemia develops and antibody titer is low.

3. If infecting strain is a non-Group A organism.

(a) Isolate patient.

(b) If clinical signs and symptoms indicate a definite infection, give sulfanilamide in the above dosages. (There is very little clinical or experimental evidence regarding the susceptibility of non-Group A strains to sulfanilamide. Preliminary results on Groups B, C and G infections in mice seem to warrant further trial in human infections.[1] Infections of the urinary tract with Group D strains are not influenced by the drug.[1])

(c) Nothing is known at present about immunotransfusion in such cases, but theoretically immunotransfusion would be desirable in the presence of bacteriemia with low antibody titer if an immune donor could be found.

B. During the puerperium

Follow the plan of treatment exactly as outlined above, with the exception of Section A 2,—i.e., removal of focus of infection. To recapitulate: In puerperal streptococcal infections, give sulfanilamide, give immunotransfusion according to the criteria previously enumerated, and give erythrogenic antitoxin in the presence of marked symptoms of toxemia (cutaneous rash, sustained elevation of temperature, persistently rapid pulse). With regard to immunotransfusion, since *small* amounts of antibody seem to be highly effective in conjunction with large doses of sulfanilamide, much time can be saved by doing the following routinely. Type 10 donors, out of these select the ones having the highest phagocytic indices relative to the patient's phagocytic index, and transfuse as often as necessary with the blood of these donors.

SUMMARY

1. A method of treatment of the streptococcal infections of pregnancy and the puerperium based on the most recent experimental observations on the hemolytic streptococcus is presented.

2. Laboratory methods for the rapid isolation and grouping of hemolytic streptococci together with the technique of immunotransfusion are outlined.

The authors wish to express their appreciation to Dr. M. H. Dawson, Dr. Champ Lyons and Dr. J. Howard Brown for permission to reprint the techniques contained in the appendix: to Dr. Rebecca Lancefield and Dr. Dawson for personal advice and assistance; to Dr. Chester Keefer for aiding in the preparation of this manuscript.

APPENDIX

I. *Laboratory Procedure for the Rapid Isolation of Beta Hemolytic Streptococci.*—

A. Direct isolation

1. Inoculate a tube of blood broth with the swab taken directly from the infected area. (Cervical or intrauterine cultures rather than vaginal ones should *always* be taken whenever possible.) Rub swab over one corner of two blood agar plates and streak for isolated colonies. Incubate one plate aerobically and the other anaerobically.
2. Incubate blood broth three to four hours, then:
   (a) Plate out a loopful on a blood agar plate, streaking to obtain isolated colonies. Incubate overnight.
   (b) Dilute serially in sterile broth to 1/100,000, beginning with 0.1 c.c. of undiluted culture. Add 0.1 c.c. of the 1/10,000 and the 1/100,000 dilutions to sterile petri dishes. Then add melted blood agar, mix and cool. Incubate overnight and examine for beta hemolysis.
   (c) Allow blood broth culture to incubate over night.
3. Examine blood agar streak and deep pour plates for presence of beta hemolytic streptococci.
   (a) If found in pure culture
      (1) Note character of growth in broth. In general, mucoid strains grow diffusely in broth, smooth strains diffusely or granularly, and rough strains flocculently.
      (2) Streak out a loopful of the blood broth culture on a Dawson plate (see Appendix II) and incubate fifteen to eighteen hours. Then examine for type of colony—mucoid, smooth or rough—with a Zeiss colony microscope. Mucoid colonies are large (up to 0.5 cm. in diameter), dome-shaped in contour, regular in outline, and their surface is smooth, glistening and watery in consistency. Smooth colonies are smaller (2 to 3 mm. in diameter), slightly opaque, whitish, fairly regular in outline and their surface is glossy and finely granular. Rough colonies are large (up to 1.0 cm. in diameter), grayish, irregular in outline and their surface is dull, coarse and uneven. Excellent photographs of the various colonial types are reproduced in the paper by Dawson, Hobby and Olmstead.[6]
      (3) Inoculate 5 c.c. of broth containing 1 per cent dextrose* with one loopful of the blood broth culture. Incubate eighteen to twenty-four hours and use as the antigen for grouping (see Appendix III).
      (4) Inoculate a tube of 25 to 50 per cent horse serum neopeptone water with 0.1 c.c. of the blood broth culture. Allow to grow two to two and one-half hours, or until first cloudiness appears, and then do capsule stain as follows. On a clean glass slide mix together one loopful of culture with one loopful of rabbit or human blood, and spread over slide with the edge of

*Media containing dextrose should never be used in the isolation and identification of hemolytic streptococci except in this instance and in the preparation of the special blood agar plates, as noted below.

another slide, as in making a blood smear. Allow to dry and stain with Wright's stain. Encapsulated organisms are best seen along the edges of the smear. Mucoid organisms are encapsulated while smooth and rough are not. This same two- to two-and-one-half-hour culture may be used in the determination of the antibody content of the patient's blood (see Appendix IV).

(b) If not found in pure culture

(1) Fish beta hemolytic colony from blood agar plate, transfer to 20 per cent horse serum neopeptone water and incubate three to four hours. From then on, proceed as outlined under Section 3a, substituting this culture for the blood broth culture.

B. Indirect isolation (if beta hemolytic streptococcus is picked up on routine vaginal culture).

1. If found in pure culture, proceed as outlined in Section A 3a.
2. If not found in pure culture, proceed as outlined in Section A 3b.

II. *Preparation of Blood Agar Plates by the Method of Dawson, Hobby and Olmstead.**—

To 3 pounds chopped beef, add 3 liters water. Extract in ice box over night. In the morning, boil for fifteen minutes. Then filter through cloth or cotton towel. Add 12 gm. of sodium phosphate ($Na_2H\ PO_4$). Heat to boiling. Add 2 N NaOH to pH 8.0 (55 c.c.). Boil thirty minutes. Add sufficient water to 3 liters. Readjust to pH 8.0. Boil fifteen minutes. Add 45 gm. of agar, and dissolve. Add 30 gm. of neopeptone (Difco). Readjust to pH 7.8. Flask in 170 c.c. amounts (250 c.c. flasks). Autoclave at 15 pounds for twenty minutes. To each 170 c.c. of agar, add 1.7 c.c. of 20 per cent solution of sterile dextrose and 4.25 c.c. of rabbit (or horse) blood. Pour about 35 c.c. of mixture over a layer of cold infusion agar in a petri dish. This will give 5 plates for each flask. Use fresh, moist plates (not later than two or three hours after pouring).

III. Grouping of Hemolytic Streptococci by the Method of Brown.[33]—

Preparation of the Antigen: The culture is grown in 5 c.c. of infusion broth containing 1 per cent of dextrose for from eighteen to twenty-four hours at 37° C. Many strains grow in the form of a sediment at the bottom of the test tube; others need to be centrifuged. All but about 1 c.c. of the supernatant broth is pipetted off and discarded. Two drops of metacresol purple indicator (0.04 gm. dissolved in 60 c.c. of 95 per cent alcohol and then diluted to 100 c.c. with distilled water) are added to the remaining sediment suspension. From a drop bottle, 2 per cent hydrochloric acid (about 6 per cent concentrated hydrochloric acid) is added, until the indicator turns slightly pink (about pH 3.0). The tube of sediment is heated in a boiling water-bath with occasional shaking for fifteen minutes and then cooled in running cold tap water for ten minutes. From a drop bottle, 2 per cent sodium hydroxide is added until the color of the indicator passes through yellow and just begins to darken (about pH 7.5), but should not be noticeably purple. The tube is then centrifuged for about fifteen minutes and the clear supernatant used for the precipitin test. I have not found it necessary to dilute the antigen.

Technique of the Test: On the bottom surface of a nearly optically perfect petri dish (a satisfactory brand of such dishes is known as "Plano") rule 12 mm. squares by means of a wax or diamond pencil. On the abscissa indicate the serums to be used; e.g., A, B, and C. On the ordinate indicate the antigens. Both inside and outside surfaces of the bottom of the petri dish must be very clean and free from lint, dust and finger prints, but need not be sterile. Within the appropriate squares and on the inside surface of the bottom of the dish, place one small (2 mm.) platinum loop of antigen and one loop of serum, mixing the serum with the antigen as added, so as to make rather flat hanging drops when the dish is inverted. A platinum loop is specified because some of the cheaper substitutes give off alkali. To avoid carbon particles in the drops, it is essential to burn off the loop thoroughly, preferably after dipping it into water to remove most of the serum each time before

*Personal communication.

flaming. It may be necessary to centrifuge the serums occasionally to free them from any particles of native precipitate. One should be careful not to form a precipitate by introducing a hot loop into the serum or antigen. Into the lid of the petri dish is placed a disk of moist, but not too wet, white filter paper. With the bottom uppermost, the bottom is placed into the lid of the dish.

Reading of Results: The assembled Petri dish is placed bottom up on the stage of a microscope, and the drops are observed through a 16 mm. objective. The optimum illumination for observing particles of precipitate is secured by closing the diaphragm of the condenser until a small (about 2 mm.) spot of light appears on the moist filter paper beneath the drop. With very little experience there need be no question about the interpretation of results. One soon learns to distinguish particles of foreign matter from the specific precipitate. In the serums which I have used, the result is usually apparent within 15 minutes, and in one hour at room temperature, it is fully developed. I have refrigerated the plates over night as a matter of routine, but found no advantage in doing so.

IV. Typing and Selection of Immune Donors for Immunotransfusion by the Method of Lyons.[15]—

1. *Determination of Antibacterial Antibody in the Blood of Patients:* About 8 c.c. of blood is withdrawn by aseptic venipuncture and defibrinated by shaking in a flask with glass beads; 0.25 c.c. of blood is measured into a sterile pyrex glass tube 5 cm. long and 9 mm. wide. One drop (about 0.03 c.c.) of a young culture of the streptococcus to be studied is added, the tube sealed in an oxygen flame and rotated for thirty minutes at 16 revolutions per hour at 37° C. The tube is then flamed and broken open, and one drop of the contents smeared as a blood film. This is stained with Wright's stain and examined with the oil immersion lens. A count is made of the number of intracellular streptococci contained in 25 polymorphonuclear leucocytes and the percentage of cells taking part in the phagocytosis is noted. A control slide is usually made from a similar preparation in infant's blood, but this control may be replaced by cultural tests after a little experience.

The bacteria for the phagocytic test are prepared by inoculating one drop of a sixteen-hour broth culture into 4 c.c. of 50 per cent horse serum neopeptone water and incubating until the first clouding occurs, usually from two to four hours.

2. *Selection of Donors for Immunotransfusion:* The blood serum from each of the prospective donors is centrifuged free from cells. To 0.25 c.c. of the patient's blood is added one drop of a given donor's serum. Tubes are so prepared for each prospective donor. The bacteria are added as before, and the test is repeated. The slide showing the greatest amount of phagocytosis indicates the desired donor.

*V. Method for Determining the Bactericidal Power of Patient's Blood.**—

Into each of 6 sterile pyrex glass tubes 5 cm. long and 9 mm. wide is measured 0.25 c.c. of whole defibrinated blood from the patient. Care should be taken not to get any blood on the upper part of the tube, as it would be charred when the tube is later sealed. A six- to eighteen-hour 5 per cent horse serum neopeptone culture of the patient's organism is diluted serially in broth from 1/10 through 1/1,000,000. Beginning with the 1/1,000,000 dilution, *one* drop of each dilution is carefully introduced with the same capillary pipette into each of the pyrex tubes containing the patient's blood. At the time the first drop of the 1/1,000,000 dilution is added to the blood, one drop of the same dilution is introduced into a sterile petri dish from the same capillary pipette. A tube of melted blood agar is added to the petri dish, mixed, cooled and incubated over night. In this way, the number of cocci added to each tube can be estimated. The pyrex tubes are sealed in an oxygen flame, put into a rotating box (for details of this apparatus the reader is referred to Ward's[34] paper) and incubated at 37° C. for twenty-four hours. At the end of this time, the tubes are broken open, the contents mixed well with a capillary pipette, and one drop from each tube is streaked out on a blood agar plate. The plates are incubated over night and the presence or absence of growth is noted on the following day.

*This technique was originally described by Todd[11] and later was modified by Ward.[34] The method as outlined here is a further modification by the authors.

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TOXEMIA OF PREGNANCY*

Types, Etiology, and Treatment

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THE term "toxemia of pregnancy" has served for generations and still serves as a diagnostic wastebasket to cloak ignorance. Medical prepossession with mysterious and unidentified "toxins" has prevented intelligent study of the various disorders combined under this misnomer. However, writers have wisely refrained from defining what toxemia is. To each the word carries certain connotations; rarely does it mean quite the same thing to any two. The late John Whitridge Williams[1] years ago pointed out that totally different pathologic conditions may be accompanied by identical clinical manifestations and, further, that classification could not be based upon the occurrence of urinary abnormalities, hypertension, coma, or convulsions. Zimmerman and Peters[2] and others more recently have shown that at necropsy patients with identical clinical syndromes may show widely varying or no significant pathologic lesions. There remains, however, one simple method of dividing this heterogeneous group of "toxemic" women into at least two main classes, and that

*Read at a meeting of the New York Obstetrical Society, January 10, 1939.

is by studying the state of affairs antecedent and subsequent to the "toxemia." Such study reveals the fact that about 80 per cent of the women designated as having "toxemia" actually have chronic vascular or renal disease before and after the gravid state, and an additional 5 per cent have such disease in acute form (Table I). However, the remaining

TABLE I. APPROXIMATE INCIDENCE OF VARIOUS DISORDERS IN WOMEN ADMITTED AS "TOXEMIA" OF PREGNANCY

	PER CENT
"Essential hypertension"	60
Chronic nephritis (including glomerulonephritis, pyelonephritis, and polycystic kidneys)	20
Acute nephritis (usually pyelonephritis)	5
Water-retention toxemia	15

15 per cent of such women have had no demonstrable abnormality before pregnancy nor after the pregnancy in which abnormalities called "toxemia" occurred. Further, these women under proper management will have subsequent uneventful pregnancies. It is this group for which the designation "water-retention toxemia" seems appropriate.

CLINICAL ASPECTS

The clinical picture manifested by these women is characterized, first, by the absence of apparent abnormalities before gestation and after the puerperium and, second, by a fairly typical course. In the last trimester of pregnancy a rapid gain in weight, generally but not always manifest as edema, is followed by a rising blood pressure, albuminuria, and later symptoms such as headache, visual disturbances, vertigo, epigastric pain, convulsions, and coma. The urine is generally of high specific gravity and does not contain red blood cells or white blood cells until the disorder has existed for some days at least. The nonprotein nitrogen and the icteric index are always normal or lower than normal until the condition is far advanced. The retinal arteries *never* show the changes that are observed so commonly in women with chronic vascular or renal disease. It is to be emphasized that these cases comprise only one-sixth of the total so-called "toxemias," and that the typical clinical course is not necessarily diagnostic. Other conditions may simulate it closely.

WATER METABOLISM

Formerly water retention in pregnancy was considered of "toxic" origin; later the pituitary antidiuretic hormone became the culprit. Now the fashion is to incriminate other, newer hormones. Evidence for these indictments, or for changes in the upper or lower urinary tract being primarily responsible, is lacking.

Almost half a century has elapsed since Starling[3] first postulated the mechanism of water exchange between the blood plasma and the tissue spaces. He indicated that the colloid osmotic pressure exerted by the plasma proteins was the force which prevented the intracapillary hydrostatic pressure from filtering water out of the blood. If one could per-

fuse an intact human being with a protein free plasma at normal intracapillary pressure it would require approximately ten seconds to filter out the entire water content of the plasma through the 6,300 square meters of surface presented by the capillaries of an average size man. However, the problems of water metabolism involve many other factors. At any level of plasma proteins, the administration of a few grams or more of sodium will cause water retention, and the withdrawal of sodium from the diet will cause water to be lost. This is true both for man and laboratory animals. It is only the magnitude of the change which varies inversely with the level of the plasma protein osmotic pressure. Furthermore sodium, although the most important substance, is but one of the electrolytes involved in water exchange. An increased potassium intake favors sodium and water excretion, and a low potassium intake probably favors water and sodium retention. The administration of any of the salts which result in an excess of negative ions in the body, such as ammonium chloride and nitrate, calcium chloride, or magnesium sulphate, causes sodium and water to be excreted.

The oral administration in large quantity of a freely diffusible organic solute such as urea, other factors being kept constant, will result in a loss of water and salt, as will the intravenous administration of hypertonic glucose or a nonmetabolizable sugar such as sucrose.

A restricted intake of water tends to cause a loss of body sodium and other salts in order to prevent concentration of the electrolytes in the body fluids. A great increase in water ingestion without an increase in electrolyte intake may actually flush out sufficient salts in the urine to result in subsequent depletion of the body fluids and later dehydration.

Other factors being kept constant, the loss of salt and water in increased sweating or diarrhea may result in dehydration.

Anemia, for some unknown reason, is conducive to water retention, as is also increased capillary permeability, such as is encountered in acute glomerular nephritis. Any process which raises the intracapillary pressure, such as congestive heart failure or venous obstruction, favors water retention. Changes in the dietary constituents, as for example the amount of carbohydrate ingested, may influence water exchange. Primary renal failure is but rarely involved in the causation of edema, which most generally depends on "pre-renal deviation." It is thus apparent that water exchange is a complex phenomenon dependent on many factors, any one of which can be studied, provided the remainder are kept constant.

In the nonpregnant subject or animal, as noted above, the magnitude of the water gain or loss following an alteration in electrolyte intake, varies inversely with the level of the osmotic pressure exerted by the plasma proteins, the albumin fraction being four times as osmotically active as the globulin fraction. The determination of the total plasma protein is therefore of no value unless the separate fractions are measured. Nor are these determinations of value unless done by an accurate method by an experienced and competent individual. Refractometric and specific gravity determinations are nearly useless as a means of estimating the colloid osmotic pressure of the plasma proteins.

WATER METABOLISM IN THE LAST TRIMESTER OF PREGNANCY

The following observations were all made in the last trimester of gestation upon women who were in the hospital but not confined to bed. They comprised both normal pregnant women and those with various types of "toxemia." None had acute glomerulonephritis, congestive heart failure, or anemia. No observations were begun until after the women had stabilized their water balances over a period of at least three days on the ward during which time salt and water were allowed freely but no saline cathartics or bicarbonate of soda were given. Twenty of the women were then given 6.3 gm. of sodium daily, either as 16 gm. of sodium chloride or 23 gm. of sodium bicarbonate in addition to the salt in or on their food. Water was allowed freely. Each of these women

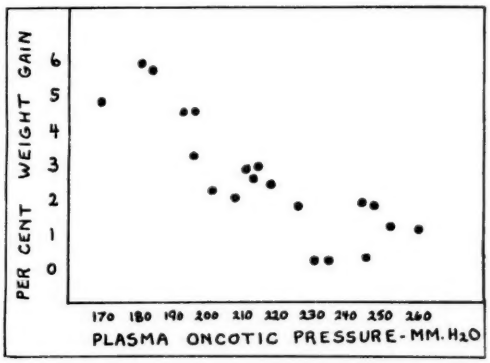

Chart 1.—The percentage body weight gain in three days plotted against the osmotic pressure of the plasma proteins in 20 women in the last trimester of pregnancy who received 6.3 gm. of sodium daily in addition to that taken in or on their food.

retained water as illustrated by their weight changes which are plotted (Chart 1) against their respective plasma protein osmotic pressures. The excellent linear correlation excludes the necessity of involving hormones, hydronephroses, or toxins to explain why some women gained 10 or more pounds and others but one or two. The limiting factor clearly appears to be the plasma protein osmotic pressure.

The converse of these observations was then carried out. Thirty women were deprived of sodium. This was most simply accomplished by arranging that their food consisted each day of only 1,500 c.c. of skimmed milk. Water was allowed freely. Fifteen hundred cubic centimeters of skimmed milk contains but 0.5 gm. of sodium and 2.0 gm. each of potassium and calcium. Each of these women lost weight as a result of moderate to extreme water diuresis. At most, 1 to 2 per cent of the weight loss can be accounted for by an insufficient caloric intake. The amount lost in five days, plotted again as the percentage of original body weight, varied in linear correlation inversely with the plasma protein osmotic pressure (Chart 2). Those women who had visible edema (about half of the group) lost all trace of this. Again there is no need of

invoking toxins, hormones, or renal disturbances to explain these changes in water metabolism.

It is thus apparent that in these cases of both normal and "toxemic" pregnancy, in the absence of severe anemia, congestive heart failure, and acute glomerulonephritis, water retention, depend essentially on the level of the plasma protein osmotic pressure and the electrolyte intake. These observations must not be construed as meaning that every instance of water retention in pregnancy is due to alterations in these two factors, nor must one factor be considered of greater importance than the other. However, it may be stated that water retention in pregnancy does not differ from water retention in the nonpregnant.

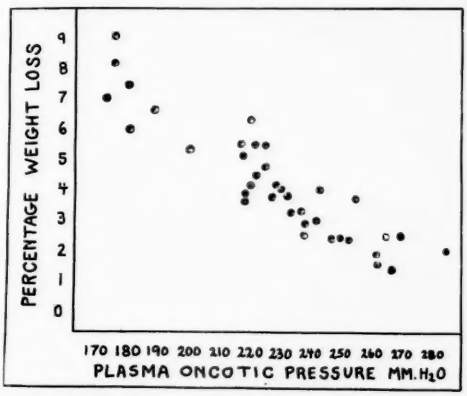

Chart 2.—The percentage body weight loss in five days, plotted as in Chart 1, in 37 women in the last trimester of pregnancy who received 1500 c.c. of skimmed milk daily but no other food. Water was allowed freely.

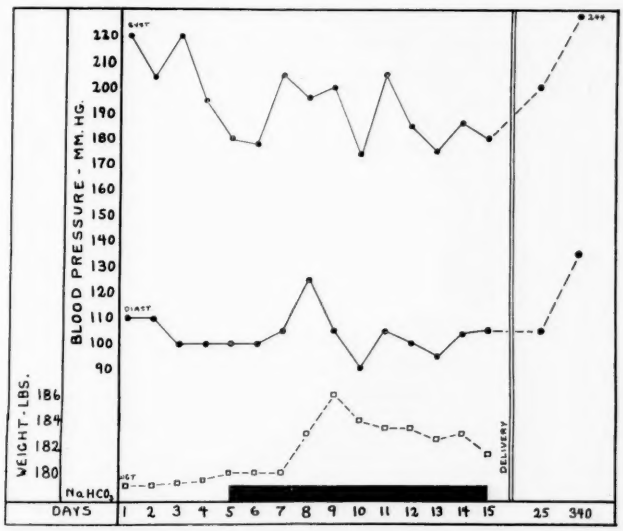

Chart 3.—The lack of effect of sodium administration in a pregnant woman with essential hypertension and a plasma protein osmotic pressure of 230 mm. H_2O. Note the continued hypertension after parturition.

THE EFFECT OF CHANGES IN WATER BALANCE ON BLOOD PRESSURE

What is the effect of changes in water balance on arterial hypertension, albuminuria, and pre-eclamptic symptoms? First were studied 10 women in the last trimester of gestation who had normal plasma proteins and either normal blood pressures or known pre-existing "essential hypertension." Chart 3 is characteristic of this group. The administration of the stated amount of sodium resulted in small increments of water retention but was without effect on the arterial blood pressure, urine, or symptoms if any existed.

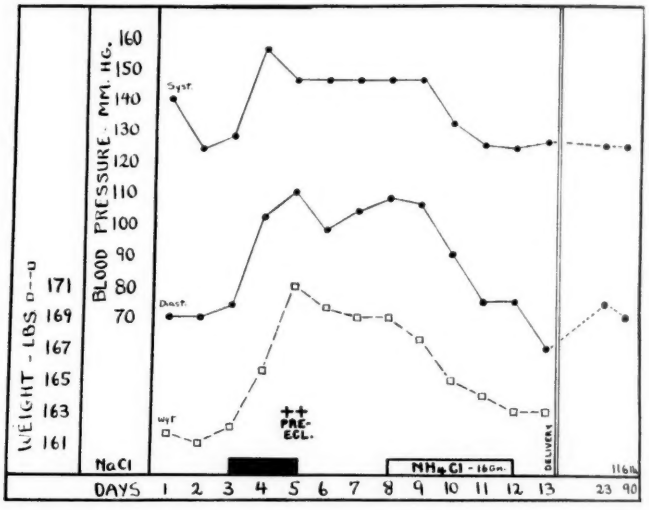

Chart 4.—The effect of sodium administration in a pregnant woman with a plasma protein osmotic pressure of 193 mm. H_2O. Note the development of acute arterial hypertension and pre-eclamptic symptoms. Generalized edema appeared. No remission occurred during 3 days after sodium was stopped. The administration of 16 gm. of ammonium chloride daily resulted in prompt diuresis and the return of the arterial blood pressure to normal. Symptoms and edema disappeared. Note normal blood pressure after the puerperium.

In contrast to these observations those made on 10 patients with low plasma proteins are illustrated by a characteristic case in Chart 4. In these patients, the administration of sodium resulted in significant gains in weight, the occurrence of obvious edema, hypertension, increasing albuminuria, and in three instances such pre-eclamptic symptoms as headache, visual disturbance, vertigo, and epigastric pain. Further, when retained water could be eliminated as shown in the chart all these manifestations subsided.

This set of observations represents as far as I am aware the first successful attempt to produce "toxemia" of pregnancy. However, I am sure that many obstetricians can recall patients whose acutely developing "toxemia" followed on a period of heartburn, self-treated with baking soda, or after a fine shore dinner rich in sodium chloride. I have personally observed 11 patients who self-treated their heartburn with bicarbonate of soda, citrocarbonate, or with a patent medicine rich in alkaline salts, only to develop edema, hypertension, albuminuria,

and, in a few instances, convulsions. In one patient no other treatment than the omission of the self-administered soda resulted in complete remission of all signs and symptoms.

The converse of these observations has also been carried out. Twenty-five women in the last trimester of pregnancy suffering from essential hypertension or chronic nephritis (including one case of congenital polycystic kidneys) have been deprived of sodium by means of the skimmed milk regime noted above. No beneficial results were observed. Chart 5 is characteristic.

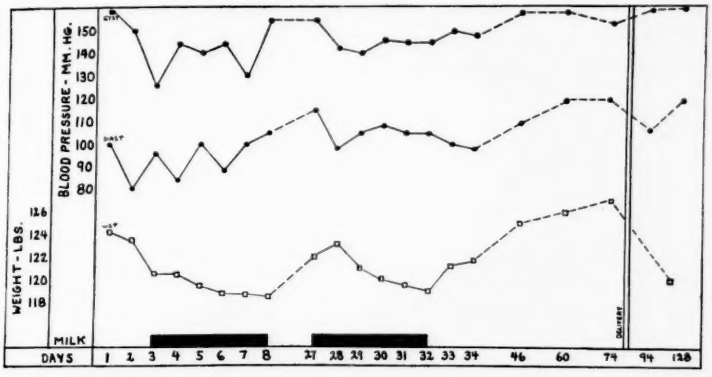

Chart 5.—The lack of effect on blood pressure of a low sodium regime (1,500 c.c. of skimmed milk daily) on two occasions in a pregnant woman with congenital polycystic kidneys. Note continued hypertension months after delivery. Plasma protein osmotic pressure 247 mm. H_2O.

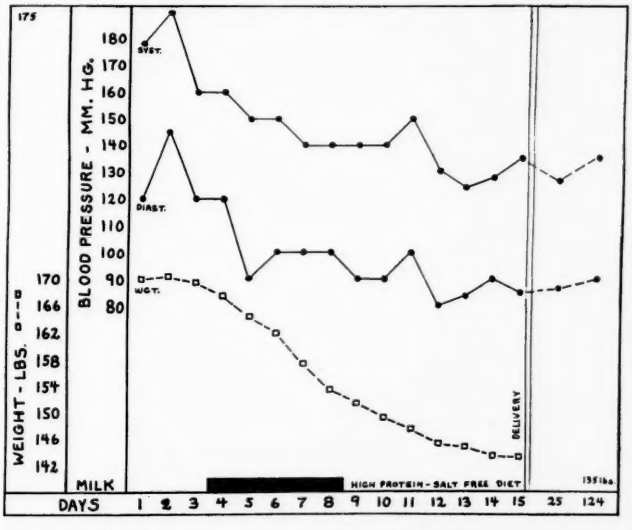

Chart 6.—Marked fall in blood pressure during low sodium regime in moderately severe case of water retention "toxemia" of pregnancy. Note the stationary weight and blood pressure during the control period before the milk regime was commenced, and that the weight remained down and the blood pressure normal while the patient received a diet containing 150 gm. protein and essentially no salt; postpartum the blood pressure remained normal. The plasma protein osmotic pressure was 175 mm. H_2O.

In contrast to such data are the results obtained in a similar-sized group of women with acute "toxemia" conforming to the clinical and laboratory picture noted earlier under the heading, "Clinical Aspects." These women all had lower plasma proteins than normal but did not have extremely low levels. The data for one case are given in Chart 6 and are characteristic for this group. Diuresis was accompanied by the disappearance of edema and pre-eclamptic symptoms, and the return of the blood pressure to the normal range. All these women had normal blood pressures and negative urinalyses when rechecked several months after delivery.

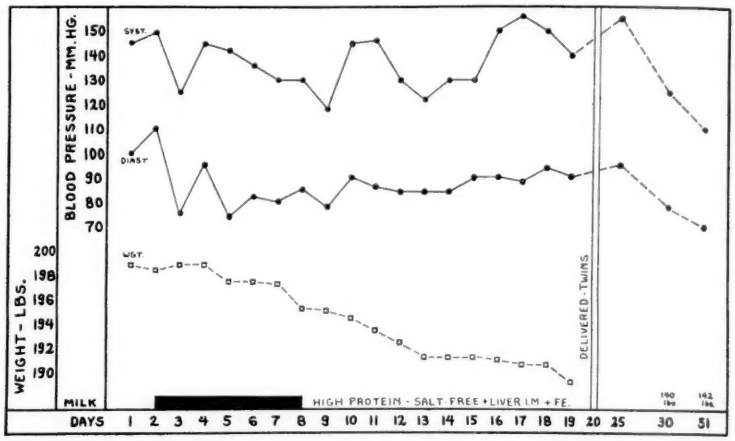

Chart 7.—The lack of effect of a low sodium regime (milk diet) in a patient with a very low plasma protein osmotic pressure (158 mm. H_2O) and severe anemia (Hg = 45 per cent). Although this patient lost 9 pounds in seventeen days she continued to have massive edema and hypertension. Following delivery the total weight lost in ten days was 50 pounds. Coincidental with this the blood pressure fell to normal.

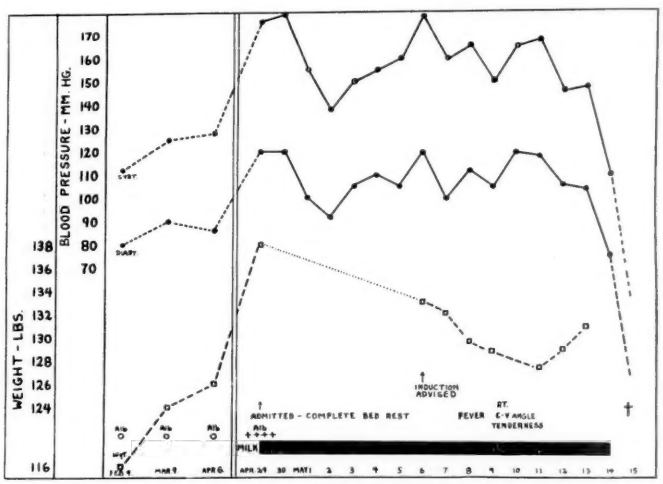

Chart 8.—The lack of effect of a low sodium regime in a patient with acute pyelonephritis. See text.

It thus appears that one may not only produce this type of "toxemia" by administering sodium but one may relieve it by eliminating sodium, if this results in a loss of retained water. However, if the plasma protein level is extremely low, significant diuresis cannot be produced in non-pregnant subjects by such a procedure. This is likewise true in pregnancy. Chart 7 illustrates the course of events in a woman who continued to have massive edema in spite of sodium restriction, and who showed no beneficial effects from the regime.

Furthermore one may have additional complications as shown in Chart 8.

This patient, a primipara, appeared normal on her first three visits to the prenatal clinic. Three weeks after the last visit she was admitted with edema, hypertension, and albuminuria, having gained 12 pounds in three weeks. It is of interest, however, that the urinary sediment showed many white blood cells and a few red blood cells. The milk regime and complete bed rest did not benefit her. Induction of labor was advised but refused. Following this she developed fever and later slight costovertebral angle tenderness. Pyelograms were made (by Dr. Benedict F. Boland) which showed marked dilatation of the right ureter and renal pelvis. Death occurred as a result of aspiration of stomach contents under anesthesia at parturition. The necropsy revealed an extensive acute right pyelonephritis with multiple cortical abscesses, and a normal left kidney. Whether this case represents: (1) water-retention toxemia complicated by acute pyelonephritis, (2) acute pyelonephritis complicated by water-retention toxemia, or (3) acute pyelonephritis alone, cannot be stated definitely. It does, however, illustrate the extreme difficulty of differential diagnosis which may occur.

THE EFFECT OF WATER-RETENTION "TOXEMIA" ON SUBSEQUENT PREGNANCY

Patients with chronic vascular or renal disease during one pregnancy will manifest these disorders not only after parturition but also in the

TABLE II. THE EFFECT OF PROTEIN AND SODIUM CONTROL ON THE SUCCEEDING PREGNANCY IN 10 WOMEN WITH WATER-RETENTION TOXEMIA

NUMBER	PREGNANCY WITH TOXEMIA			SUCCEEDING PREGNANCY* NO TOXEMIA		
	MAXIMUM BLOOD PRESSURE MM. HG		PLASMA PROTEIN OSMOTIC PRESSURE MM. H_2O	MAXIMUM BLOOD PRESSURE MM. HG		PLASMA PROTEIN OSMOTIC PRESSURE MM. H_2O
	SYST.	DIAST.		SYST.	DIAST.	
1	146	110	182	120	80	248
2	172	116	180	116	84	252
3	170	110	218	130	80	235
4†	190	145	175	130	90	241
5†	172	112	192	124	82	242
6	170	120	–	130	85	242
7	206	120	–	126	80	219
8†	170	100	–	104	60	–
9†	170	115	183	130	90	215
10	162	120	120	110	70	204

*Patients 1 to 6 were given an adequate protein intake without salt restriction; Patients 7 to 10 also were maintained on low salt diets.

†Fetal death occurred in Cases 4, 5, 8, and 9 in the "toxemic" pregnancy. There was no fetal mortality in the succeeding pregnancy.

In the "toxemic" pregnancy each of the 10 women had albuminuria and pre-eclamptic symptoms. In the next pregnancy the patients were asymptomatic and did not have albuminuria.

next pregnancy. Patients with water-retention "toxemia" are prone to have recurrence unless special attention is paid to their protein and electrolyte intake in the next pregnancy. Ten such women have been followed through two pregnancies. They all had hypertension in the pregnancy for which they first were under observation. Four fetal deaths occurred. In the next pregnancy a high protein intake was commenced early. In spite of this an abnormal lowering of the plasma proteins occurred in three. These women were then maintained on a salt-free regime. None of the 10 developed any manifestations of toxemia. Ten healthy babies were delivered. The maximum blood pressures in the two pregnancies are shown in Table II.

It thus appears that water-retention toxemia need not recur in subsequent pregnancies if adequate attention is paid to diet and electrolyte intake.

DISCUSSION

Sixty-five years ago Rosenstein stated his belief that eclampsia resulted from the effusion of serum out of a "too-watery" blood. Many methods of treatment of "toxemia" which have met with more or less success, have knowingly or unknowingly been measures to eliminate water retention. The use of purgation with magnesium sulphate to rid the body of "toxins" is a double means of ridding the body of water, first by direct loss from the bowel, second by the acidifying diuretic action of the absorbed sulphate ion. The adherents of the belief that "toxemia" arose from hypocalcemia have administered calcium chloride, an excellent acidifying diuretic. Fluid restriction popularized by Arnold and Fay[4] is obviously aimed at the loss of water. An exceedingly large intake of water, as noted above, may lead to actual diuresis above the amount ingested. Hypertonic glucose solutions given intravenously are dehydrating. Starvation results in a loss of salt and water. A high protein intake may be diuretic because of the increased urea excretion. If the high protein intake is achieved by a large ingestion of meat there will be a relatively high potassium and low sodium intake. A milk regime achieves similar ends.

Why, then, have these methods failed to meet with universal success in the treatment of "toxemia"? First and foremost is the fact that 85 per cent of the cases of so-called toxemia are unrelated to water retention. This fact cannot be stressed too strongly. Second, many cases of water-retention toxemia have plasma-protein levels so low that no method will achieve significant water loss. Third, cases of water-retention toxemia may be complicated by other factors as noted above. Fourth, all methods of ridding the body of excess water are not equally successful and may have harmful side effects. Last, since the aim of the obstetrician has not been clear, he not infrequently has employed measures which counteract each other. The commonest of these is the employment of a salt-free diet, while saline solutions are being given under the skin or intravenously, or bicarbonate of soda by mouth.

Although the most satisfactory clinical measure of water balance is the weight curve, it is to be remembered that all undue gains in weight

are not dependent upon water. I have seen two patients during pregnancy gain 50 and 72 pounds, respectively, not because of water retention but from true fat accumulation. A low sodium regime was obviously ineffective in ridding the body of excess of fat.

The doctrine that there is a critical level of the plasma proteins below which edema occurs was a necessary stage in the development of our knowledge. However, we have seen patients with plasma proteins far below this level who had no edema because they did not ingest the necessary salt and water to allow the formation of edema. On the contrary, other patients, because of a very large intake of salt and water, have developed generalized edema with plasma proteins well above the so-called critical level.

Why some patients may have rather marked water retention without arterial hypertension is unknown. In a number of instances marked water retention has been observed for a period of several weeks before arterial hypertension developed, and in others parturition has supervened without hypertension ever appearing. Whether these women would have eventually developed hypertension had pregnancy continued longer cannot be said. Although there is no evidence for such a belief, it is possible that some individual or constitutional susceptibility to hypertension is necessary in order that water retention may produce hypertension during pregnancy.

It is to be remembered that although a low sodium regime may free the patient of retained water, result in a fall of arterial blood pressure to normal, and cause headache, drowsiness, vertigo, and visual disturbances to disappear, such a regime does not alter the fundamental disturbance: hypoproteinemia. These patients remain in unstable equilibrium as long as the plasma colloid osmotic pressure remains at a level at which it is constantly in danger of being overbalanced by the intracapillary hydrostatic pressure. "Cure" is not effected until the plasma proteins have returned to normal. Since "toxemia" occurs late in pregnancy, when fetal demands for protein are large, and since hypoproteinemia probably signifies not only a low plasma protein level but also a depletion of the organism's reserve stores of protein, one must not expect a rapid increase in plasma protein values during the remainder of gestation even with intensive protein feeding. It is possible that the intravenous infusion of concentrated plasma protein ("lyophile" serum) may be of value. However, any procedure which alters the blood volume of such patients may upset their unstable equilibrium and precipitate serious results.

A question which inevitably must arise is whether nonpregnant individuals with similar hypoproteinemic edema show the same phenomena regarding blood pressure as do these women. It is true, of course, that the usual type of nonpregnant patient with hypoproteinemia seen in American hospitals suffers from cirrhosis, nephrosis, anemia, tuberculosis, colitis, or other debilitating disease which may alter the reactivity of his vascular system. However, it appears probable that certain peculiarities of the pregnant state itself may be responsible for this unusual behavior of the vascular system to water retention. Some of the known physiologic alterations which are present in pregnancy are a 40 per cent

increase in blood volume, a 50 per cent increase in cardiac output, a moderate elevation of venous pressure, and probably moderate mechanical pressure by the enlarged uterus on the ureters and on the renal veins. Although various tests fail to reveal any consistent changes in renal function in "toxemia" of pregnancy, the fact that albuminuria is generally present in itself indicates that there is a disturbance of the kidney even though histologic examination fails to reveal anything more than cloudy swelling. The real nature of this disturbance and its possible relationship to the occurrence of hypertension as a result of water retention are unknown. The role of hormonal changes in pregnancy is so little understood that discussion is hardly warranted. It is possible that hormonal changes make the pregnant woman unusually susceptible to changes in water balance. However, no one has yet produced toxemic manifestations by administering hormones, and a recent investigation[5] indicated that restoration of hormone values to normal failed to influence toxemic manifestations.

Since hypoproteinemia is one of the more important factors which permits the development of water retention, adequate prenatal care must include attention to the prevention of this condition. Although disturbances of absorption, assimilation, manufacture and urinary loss of protein may be involved, it appears that the chief cause of hypoproteinemia in pregnancy lies in inadequate dietary intake of protein of good biologic value, especially in view of the increased demands for protein for the developing fetus and also for the maternal organism. It is, therefore, of paramount importance that the diet in pregnancy contain more, not less, protein than an adequate diet for nonpregnant subjects. It is likewise important that the pregnant woman avoid an excessive intake of sodium salts under any conditions, and if she has low plasma proteins actual sodium restriction must be employed. Anemia, which is conducive to water retention, is to be avoided by proper prophylactic measures.[6]

CONCLUSIONS

1. The term "toxemia of pregnancy" is a misnomer. Approximately 85 per cent of patients so classified actually have primary vascular or renal disease. In such patients changes in water balance do not affect signs or symptoms.

2. A large proportion of the remaining 15 per cent are suffering from water retention. This may be due primarily to low plasma proteins or to excessive sodium intake or, in many instances, to both factors. Measures which lead to further water retention increase the severity of the "toxemic" manifestations, whereas measures which result in the loss of excessive retained water result in an amelioration of these manifestations.

3. A low sodium intake is one means of eliminating undue water retention.

4. The development of water-retention toxemia may be prevented by maintaining the pregnant woman's plasma proteins at a normal level by an adequate diet and avoiding excessive sodium ingestion.

(Detailed descriptions of the observations noted in this paper and a more complete bibliography will be found in references.[7b, d, e, g, h])

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DISCUSSION

DR. ALVIN J. B. TILLMAN.—In discussing the type of toxemia characterized by hypertension, albuminuria, with or without edema which occurs in the last trimester of pregnancy, and is frequently accompanied by headache, visual disturbances, and epigastric pain or distress, I cannot agree with the view that the edema is responsible for the toxemia. It seems to me that a very good case could be made as well for cell volume, plasma volume, serum, or albumin and globulin determinations. Dr. Strauss excludes various other factors as causative agents in the etiology of toxemia, mainly because of the existing confusion in the various fields, but this, in my opinion, is an inadequate reason for exclusion. For example, the fact that endocrinology is in a state of confusion does not rule out the possibility of hormonal imbalance in toxemia. And hypoproteinemia frequently results from the loss of protein through the kidneys, in addition to the factors mentioned by Dr. Strauss.

In the type of toxemia under discussion the first evidence of toxemia very frequently is a slight elevation of blood pressure. The question of body weight as evidence of toxemia of pregnancy seems of importance in a large number of cases, but Sidell and Mack pointed out not very long ago that in a very carefully controlled series of one hundred cases of toxemia they were unable to determine any relationship between the body weight and the severity or type of toxemia. Furthermore, in their control series of six hundred cases nearly 40 per cent also gained a tremendous amount of weight, and any etiologic factor concerned must explain the gain of large amounts of weight in the normal pregnant as well as in the toxic pregnant woman.

If I were to say to you as obstetricians that patients with pre-existing hypertension and pre-existing nephritis who became pregnant have a greater incidence of the same toxemia under discussion you might refute the argument, but if I were to ask you why you take such great care of such patients, and are so cautious about those with hypertension when they are seen early in pregnancy, you would reply that your care is first in the interest of the fetus, to prevent prematurity and fetal death, and second in the interest of the mother. In the latter case your greatest care is to avert, if possible, the appearance of the sudden onset of acute edema, increasing hypertension, albuminuria, headaches, and epigastric pain—in other words, pre-eclampsia. And the probable reason why pre-eclampsia and eclampsia are said to be more infrequent in the presence of pre-existing hypertension and chronic nephritis is because of the care that you take of the patient. This view has been stated by Thiell and Read, and I am in complete agreement with them. It seems to me, therefore, that if hypoproteinemia is responsible, it certainly must occur in the cases of hypertension during pregnancy, and to explain a specific or a water toxemia one must explain the lack of hypoproteinemia in such a situation. Furthermore, I have not infrequently observed pre-eclampsia and eclampsia with normal serum protein with edema. Patients who have had convulsions with all the enumerated symptoms except the edema cannot be ruled out of the group because of that, and dry eclampsia, as stated in the classical textbooks, is the most severe type of eclampsia.

DR. HENRICUS J. STANDER.—Plass and Mathews, in 1926, showed that pregnancy is usually associated with a decrease in the total plasma proteins, amounting to about 9 per cent. Their work has been well corroborated by many other workers,

and today it is accepted that normal pregnancy is associated with a decrease of total serum proteins of from 5 to 7 per cent.

We have done a certain number of total serum protein determinations on pre-eclamptic and eclamptic patients. Although I appreciate fully the importance of the rôle that serum proteins may play in the conduct of water balance, so far I have been unable to convince myself that a reduction in the total serum proteins is responsible for the marked increase in body weight due to water retention that we see in many cases of pre-eclampsia. You are all familiar with many cases like the one Dr. Strauss showed here where the patient's weight is normal during three or four visits to the antenatal clinic and then suddenly there is a marked increase in body weight. There seems to be some factor, of which we are still ignorant, responsible for this sudden water retention.

There is great confusion in regard to toxemias of pregnancy, although this appears to me to be unnecessary. There are two entities that must not be confused with the toxemias of pregnancy; one of them is essential hypertension, and the other, renal disease. First, essential hypertension, whether on a familial, hormonal, nervous or any other basis is a wholly different entity from what we call "toxemia of pregnancy." Second, nephritis, of whatever form, hemorrhagic, arteriosclerotic or degenerative, is likewise a wholly different disease from what we call "toxemia of pregnancy."

That leaves us only two entities: one, the eclamptic syndrome, which is eclampsia or pre-eclampsia, and the second, about which there has been so much disagreement and which I have called low reserve kidney, and which others have called hypertensive disease, vascular disease, and albuminuria of pregnancy. I do not claim that the term "low reserve kidney" is correct. It is not essential hypertension, it is not chronic nephritis, and certainly it is not eclampsia. Perhaps it may be, as claimed by Kellogg, a very mild form of pre-eclampsia.

Now what Dr. Strauss is talking about is true toxemia. By that I take it he is talking about eclampsia and pre-eclampsia, not about chronic nephritis, not about nephrosis, not about essential hypertension. The water balance in the body is an intricate and delicate mechanism. We have several factors to contend with such as the serum proteins, the electrolyte balance and the kidney.

I cannot help but feel that something should be said about the recent work on the hormones. Thorn, Nelson and Thorn have reported water retention in normal women at the intermenstrual and premenstrual periods, when the level of sex hormones is high. In dogs water retention has been induced by the administration of estrone, accompanied by increased K excretion. There appears to be enough evidence at present to ascribe to the sex hormones an ability to regulate, in part at least, the excretion of certain of the inorganic ions, Na, K, and Ca, as in the case of the adrenal cortex hormone or hormones.

I do not wish to detract from the importance of the role played by the colloid osmotic pressure, as so well shown by Dr. Strauss. The normal individual compensates for increased Na intake by increased Na excretion, whereas the person with a low colloid osmotic pressure of the blood, responds to such increased Na intake by fluid retention rather than by increased Na excretion. Here then the low osmotic pressure is primary to the balance of the electrolytes. But, in the case of pregnancy, we should also remember that after delivery retained water is very rapidly excreted, a finding which can hardly be explained mainly on the basis of changes in serum protein content, or on differences in Na intake. May this not perhaps be associated with rapid changes in the excretion of inorganic ions, dependent, in part perhaps, upon sex hormone levels in the body?

DR. ALFRED C. BECK.—If Dr. Strauss' deductions are correct, should not the greatest amount of water retention occur early in pregnancy? The most carefully conducted balance studies, including those of Barr and Merlin in the dog, show a negative nitrogen balance or at least a tendency toward the same in the first trimester. All such studies, on the other hand, show a rather marked retention of nitrogen in the latter part of pregnancy. Early in pregnancy, patients are accustomed to take an excess of sodium in the form of sodium bicarbonate. This also should favor water retention in that period.

Only recently, I had a case of twin pregnancy in which the mother was placed on a milk diet and given cathartics. The edema disappeared, the blood pressure returned to normal and she lost considerable weight. As a result, I was perfectly satisfied from the clinical standpoint but, because of her low plasma proteins, I increased the protein intake considerably. Following this, her blood pressure went up very rapidly and a very marked albuminuria occurred, with the result that I was forced to empty her uterus. I therefore believe Dr. Strauss will find, when he has a larger series, that not all patients will respond as did those reported by him this evening.

DR. GEORGE E. ANDERSON.—Dr. Strauss has considered only a small percentage of cases, representing probably 15 per cent of all cases of so-called toxemia. Probably the majority of toxemic patients are not correctly diagnosed from the internist's point of view, particularly such cases as those with low renal threshold, chronic nephritis and liver disorders.

If I understood Dr. Strauss correctly, he claims not a very marked lack of serum protein, but rather a *relative* lack which in the presence of other factors, will decide the presence or absence of edema. Certainly none of the pregnant women whom we customarily see have serum protein levels anywhere near the critical level of near 5. When you add to the condition of slightly reduced serum proteins, however, one of hypermetabolism and its attendant demand on the maternal protein economy together with the increased protein needs of the growing fetus, the increase of vascular volume and hydrostatic pressure incidental to late pregnancy, even slight changes in serum protein content will produce remarkable effects.

It is certain that Dr. Strauss' patients lost considerable of their body-weight or hidden edema when their serum proteins were increased to normal or close to normal levels. This may not have been due to an absolute increase in serum protein but a relatively increased value through sodium and water depletion. I doubt if we see the average pre-eclamptic woman long enough to treat her sufficiently to raise a low serum protein to a normal level merely through protein feeding. It is conceivable, however, that slight protein deficiency may be corrected or the ill-effects of such slight deficiency be minimized by careful attention to salt and water metabolism.

Studies of the type which Dr. Strauss has presented will eventually lead to a solution of the problem of true eclampsia. There are probably a dozen investigations which should go hand in hand with this consideration of water metabolism. The factor of liver, for example, in water metabolism has not been sufficiently stressed as a factor in toxemia or even in hypertension. We do not know the cause of capillary permeability or of the hypertension which accompanies eclampsia. Dr. Strauss presented just one factor—water retention in eclampsia in relation to salt and plasma proteins.

DR. STRAUSS (closing).—I wish to emphasize that the weight changes observed in these pregnant women occurred without change in the plasma protein level. They were brought about solely by changes in the electrolyte intake, although, as Dr. Anderson has pointed out, it is the plasma protein osmotic pressure level which is the limiting factor involved.

Dr. Stander has raised the question of hormones. They present a fertile field for speculation, almost as mysterious as the now defunct "toxins." Thus far, no one has been able to produce "toxemia of pregnancy" by administering hormones or to relieve it with either hormones or antihormones, whereas both these may be accomplished by altering the water balance.

In conclusion, allow me to state once more that approximately 85 per cent of our series of cases of so-called "toxemia" represent primary vascular or renal disorders in which pregnancy is the complication rather than the cause.

THE OBSTETRIC MANAGEMENT OF PATIENTS WITH TOXEMIA*

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THE management of pregnant patients with toxemia has been a varied one during the past few decades. The medical treatment, entailing dietary regulations, bed rest, the use of bromides, chloral hydrate, barbiturates, or the intramuscular or intravenous injection of magnesium sulphate, has been used extensively in some clinics. In other hospitals the surgical treatment (the early termination of the pregnancy either by accouchement forcé or cesarean section) has been used exclusively. The treatment of choice, namely the obstetric, should be a logical combination of both medical and surgical procedures. Since the efficacy of the treatment used can only be judged by the number of *normal* surviving mothers and babies, we shall discuss our obstetric management of toxemic patients and the results.

The hospital incidence in the United States of nonconvulsive toxemia of pregnancy varies from 0.2 to 29 per cent, average 4 per cent; and the maternal mortality for this condition ranges from 0 to 10 per cent, average 1.7 per cent. Dieckmann states that there are as many and probably more deaths from this condition than there are from eclampsia. The fifteen state mortality study revealed that 26 per cent of the maternal deaths were due to toxemia. Twenty-three per cent of these toxemic deaths occurred in undelivered women of whom 31 per cent belonged to the nonconvulsive group. The Philadelphia report indicates that 29 per cent of the deaths were associated with toxemia and that 19 per cent of the patients died undelivered. Unpublished data of ours indicate that similar figures are true for Chicago.

The uncorrected fetal mortality (abortions, stillbirths, and neonatal deaths) for several series of cases is illustrated in Table I. We have attempted to compare similar data from various articles with our results.

TABLE I

	TOTAL %	PRE-ECLAMPSIA		ESSENTIAL HYPERTENSION		VASCULAR-RENAL DISEASE	
		MILD	SEVERE	MILD	SEVERE	MILD	SEVERE
Peckham	14.9	(9.5)*	17.7			25.5	
Stander	15.8	(8.3)*	18.9			29.0	
Tillman and Watson	25.7		24.0	3.0	30.0	36.0	69.0
Present Report	12.8	6.0	12.0	6.0	21.0	12.0	37.0

*Fetal mortality for low reserve kidney.

*Read at a meeting of the Chicago Gynecological Society, January 20, 1939.

Hess states that 16 per cent of the mothers of their premature fetuses had toxemia and that 26 per cent of these fetuses died.

Clifford reports that at the Boston Lying-in Hospital 30 per cent of their premature fetuses born alive are from toxemic patients and that the mortality is 29 per cent.

Dunham and Tandy state that in 2,000 stillbirths collected from various hospitals, toxemia occurred in 25 per cent of the cases in the period from thirty-two to thirty-five weeks. Theoretically, all babies of this age should survive.

The maternal and fetal mortality of toxemia of pregnancy can be estimated, but we have no means of determining the maternal morbidity (such as vascular-renal disease or permanent injury to the pelvic tissues from forced delivery) or fetal morbidity (prematurity, intracranial hemorrhage, etc.) associated with it.

Table II lists data as to the onset of labor for several consecutive periods and also a column for the total cases. Fractions of a percentage have been dropped for obvious reasons. A medical induction of labor means that labor ensued after injections of pituitrin had been given. If the membranes were artificially ruptured and pituitrin given, the case was included under the former condition. "Operative" includes all cesarean sections, abdominal and vaginal hysterotomies, and a few therapeutic abortions by dilatation and curettage.

TABLE II. ONSET OF LABOR FOR ALL CASES

METHOD	1931-36 %	1936-37 %	1937-38 %	1931-38 TOTAL %
Normal	58	72	73	64
Induced	21	14	13	18
Pituitrin	9	10	10	9
Rupture of membranes	4	3	1	3
Intrauterine bag	6	1	2	5
Intrauterine pack	2			1
Operative	21	14	14	18
Total cases	944	223	222	1,389

An active, perhaps even a surgical, treatment of toxemia is represented by the results for 1931 to 1936. A definite trend to the obstetric management began about 1933 and is represented by the two periods of one year each. The number of patients, who had labor induced or an operative termination of the pregnancy before labor, have each decreased 33 per cent and undoubtedly each could be reduced still further. The intrauterine pack has been discarded and the bag is used only in selected cases. The reason for our change of management has been because the fetal mortality is lower and the maternal results better.

Data as to the delivery of fetuses of 1,000 gm. and more are given in Table III. The number of vaginal operative deliveries is high, but a major portion of these deliveries were in primiparas who were delivered by prophylactic forceps. As a rule, we believe that difficult operative procedures such as Dührssen's incisions are contraindicated in toxemic patients because of the prolonged anesthesia, tendency to shock, and added danger of injury to the baby. However, these incisions are of

TABLE III. DELIVERY OF FETUSES WEIGHING OVER 1,000 GM.

METHOD	1931-36 %	1936-37 %	1937-38 %	1931-38 TOTAL %
Normal	54	54	57	55
Operative vaginal	(a) 30	34	32	30
Forceps	24 (b)	29	27	25
Dührssen incision	1	1	1	1
Craniotomy	1	1		1
Cesarean section	16	12	11	15
Total Deliveries	899	219	215	1,333

Difference between (a) and the sum of column (b) represents breech extractions and podalic versions.

special value in deliveries before term where there is no disproportion and dilatation stops at 5 to 7 cm. Premature babies are especially susceptible to intracranial injury and after a suitable period of labor without progress, the cervix should be incised and the baby delivered with forceps after an episiotomy. The craniotomies were almost without exception performed on dead fetuses. The number of deliveries by abdominal hysterotomy steadily decreased, but is still too high. We prefer early delivery of the severe pre-eclamptic who is on the verge of eclampsia, and we rupture the membranes if the cervix is "ripe" (meaning that the cervical canal is obliterated and the margins soft and dilatable). If the cervix is not "ripe" and the fetus is estimated to weigh over 2,000 gm., the pregnancy is usually terminated by cesarean section. Patients with essential hypertension or vascular-renal disease, who comprise 12 and 36 per cent, respectively, of our toxemic patients, quite often require delivery at thirty-two to thirty-six weeks' gestation because of the blood pressure or large amount of albumin in the twenty-four-hour urine. At this period of pregnancy the cervix is usually uneffaced, firm, and closed. These patients should also have a tubal ligation. These various reasons, together with a lower fetal mortality, induce us to favor cesarean section.

Immediate delivery by cesarean section, because the toxemia was endangering the patient's life, was deemed necessary in only a small percentage of the cases. Over 20 per cent of the patients delivered by cesarean section had either primary or contributory maternal indications such as contracted pelvis, previous cesarean section, placenta previa, or abruptio placentae. Sterilization by tubal ligation was done for various indications in over 40 per cent of the operations. Approximately 60 per cent of the cesarean sections were performed on patients with vascular-renal disease primarily for two reasons: one, to deliver the baby, which was usually premature, with the least trauma; and the other to permit tubal ligation. Although our total incidence of cesarean section in toxemic patients has decreased, the reduction has been limited to the pre-eclamptic group.

Using criteria described in a previous paper we have classified patients as having pre-eclampsia, essential hypertension, or vascular-renal disease. Data as to the onset of labor and methods of delivery for each group are given in Table IV and illustrate how the diagnosis of the disease influences the management. Thus, if the diagnosis was pre-eclampsia, we

would favor normal delivery. If the patient had vascular-renal disease or severe essential hypertension, premature delivery and sterilization would usually be advisable. If the patient had a mild essential hypertension, normal delivery would be chosen.

TABLE IV

	PRE-ECLAMPSIA		VASCULAR-RENAL		ESSENTIAL HYPERTENSION	
Onset of Labor (Per Cent)						
Normal	70		57		70	
Induced	24		24		14	
Elective operation	6		18		15	
Therapeutic abortion			1		1	
Method of Delivery or Termination of the Pregnancy (Per Cent)						
Normal	50		58		50	
Operative vaginal	*40		15		34	
Forceps		*34		11		26
Operative abdominal	10		27		16	
Cesarean section		9		20		13
Hysterotomy		1		7		3
Per cent of all toxemias	47		36		12	

*Difference represents breech extractions, podalic versions, and craniotomies.

The figures for the two tables are not additive. That is, the same 6 per cent of the pre-eclamptic patients who had no labor but were terminated by an elective operation are included in the 10 per cent of the second part of the table. The highest incidence of abdominal delivery occurs in the vascular-renal group.

The interruption, if early in pregnancy, was solely in the interest of the mother, and if after the thirtieth week, in the interest of both mother and fetus. The babies in the vascular-renal group were usually small and a large percentage of the patients were multiparas, hence, the low incidence of forceps deliveries. The high operative termination of pregnancy is due in great part to the large number of hysterotomies on previable fetuses (less than 1,000 gm.) and cesarean sections.

The duration of labor was over eighteen hours in approximately 35 per cent and over twenty-four hours in 25 per cent of all primiparas with toxemia. Twenty-five per cent of the multiparas with toxemia were in labor over twelve hours, 10 per cent over eighteen hours, and 5 per cent over twenty-four hours. These data are at variance with statements that labors in toxemic patients are short and easy. A complicating factor is that a number of the labors were induced and they tend to be longer than normal.

The average morbidity for all the puerperal patients using the British standard is 7.8 per cent. Thirty-two per cent of all toxemic patients were morbid; 9 per cent of the patients had temperatures over 39° C. The increased incidence of fever in toxemic patients is probably the result of the increased vaginal manipulation incidental to the induction of labor and high percentage of abdominal deliveries rather than the result of decreased tissue resistance. Severe toxemia is occasionally accompanied by a hyperpyrexia.

Various data as to fetal mortality are given in Table V. There were 1,389 pregnancies and 178 (12.8 per cent) patients had no live baby on discharge from the hospital. Twin pregnancies, both babies living, have been counted as one fetus, but if one was dead, both were considered dead. Our data include all macerated fetuses and spontaneous abortions. We wished to determine what chance a toxemic patient has to obtain a

TABLE V

WEIGHT OF FETUS GM.	TOTAL GROUP			FETAL MORTALITY %		
	NUMBER	%	F. M. %	NORMAL ONSET	INDUCED LABOR	ABDOMINAL LAPAROTOMY
A. Fetal Mortality in Various Weight Groups in Relation to Onset of Labor						
1- 999	45	3	96.0	100.0	100.0	85.0
1,000-1,499	45	3	71.0	84.0	81.0	30.0
1,500-1,999	53	4	28.0	37.0	13.0	32.0
2,000-2,999	401	29	8.0	5.8	9.6	11.4
3,000-3,999	683	51	3.0	1.6	8.8	6.4
4,000	133	10	3.0	2.1	7.4	0.0
Total	1,389		12.8	6.1	15.9	16.7
Number				886.0	251.0	204.0
B. Mortality of Viable Fetuses						
Over 1,000	1,315	98	8.0	5.2	14.3	12.0
Over 1,500	1,270	95	6.0	3.6	9.1	11.0
Over 2,500	1,077	80	3.9	2.5	8.3	6.1
C. Comparison of Fetal Mortality for Three Periods						
1931-1936 Total	944		15.5	7.3	16.6	19.2
Over 1,500 gm.	851	90	6.8	4.5	9.6	12.2
1936-1937 Total	223		7.2	2.5	12.9	7.7
Over 1,500 gm.	213	95	2.3	1.3	3.0	4.0
1937-1938 Total	223		7.2	5.4	14.3	10.7
Over 1,500 gm.	209	94	2.3	2.5	4.1	4.1

living baby. Fractions of a per cent have again been dropped unless the groups were large. Swanson, Turner, and Adair studied all fetal deaths from our hospital, including those from toxemic patients, and reported a fetal mortality for groups comparable to the first three of Table V, Part A, of 100, 73, and 22 per cent which are similar to our figures. The mortality of the viable premature (1,000 to 2,499 gm.) from toxemic mothers is 26 per cent which is higher than the premature mortality of the hospital, 19 per cent. Potter states that the fetal and neonatal mortality for all term infants, which includes babies from toxemic mothers, is 1.9 per cent which is much less than our rate of 3.9 per cent. It is obvious that toxemia is associated with a high fetal and neonatal mortality for both term and premature babies.

The effect on the fetal mortality of a normal onset, of induced labor, or of delivery by abdominal hysterotomy is demonstrated in Part A. It is obvious that patients who had a normal onset of labor were almost invariably of the mild type and that a laparotomy was used almost entirely for the severe cases. Laparotomy seems to offer the best chance for the fetus of 1,000 to 2,000 gm. and those over 4,000 gm. Induction of labor

results in a very high mortality. If the patients are properly selected, this death rate can be markedly reduced. If medical treatment can be used with safety until labor begins, the fetal mortality is lowest for babies of 2,000 to 4,000 gm.

Part B lists the fetal mortality for three weight groups. Adair considers all fetuses of 1,000 gm. or more as viable. However, although the 1,000 to 1,499 gm. group comprised only 3 per cent of all fetuses, yet the mortality of 71 per cent materially raised the average mortality. The mortality for fetuses over 1,500 gm., which includes 95 per cent of all babies, is within reason for a normal onset of labor but still far too high for induction of labor or cesarean section. The same may be said for babies over 2,500 gm.

Data in Part C are especially instructive. The staff has remained essentially the same but the comparison for the three periods demonstrates a marked reduction in the total mortality and an even more marked decrease in the rate for fetuses over 1,500 gm. for the last two years. This reduction is due to improved prenatal observation and especially to a better understanding of the indications and necessary conditions for terminating the pregnancy. The decrease in the cesarean mortality is noteworthy and is the result of better technique for the delivery of the fetus and expert treatment in our premature nursery.

The type and severity of the toxemia are illustrated by the following data. Labor was induced or the pregnancy terminated in 26, 21, and 36 per cent of patients with mild pre-eclampsia, essential hypertension, and vascular-renal disease, and 10, 21, and 21 per cent, respectively, of these fetuses were lost. Similar figures for the severe groups are 56, 52, and 67 per cent induced, and 18, 20, and 49 per cent, respectively, of these fetuses lost. Thus, the patient with severe toxemia of pregnancy, especially of the chronic type, is confronted with a poor chance for obtaining a living baby.

We have records of 18 maternal deaths. One of these followed a gall bladder operation three months post partum.

TABLE VI

PRIMARY CAUSE OF DEATH	NUMBER OF CASES WHO DIED WITHIN	
	2 MONTHS POST PARTUM	2 YEARS AFTER DELIVERY
Puerperal infection	3	0
Heart disease and/or anemia	3	1
Uremia	1	6
Cerebral hemorrhage	0	3
	7	10

The total determinable maternal mortality associated with childbirth and toxemia or vascular-renal disease over a period of seven years is 1.3 per cent. Many of these patients had a chronic disease, but the pregnancy usually aggravated the process. Our immediate mortality is 7 or 0.56 per cent of which 4 deaths were presumably preventable. There have been no immediate deaths due to nonconvulsive toxemia during the past five years. This record is the result of a proper study of each patient with toxemia.

DISCUSSION

The total fetal and neonatal mortality for the last two periods was decreased 53 per cent. There was a 66 per cent decrease for fetuses weighing over 1,500 gm. Potter analyzed all fetal and neonatal deaths in the hospital and stated that the mother had toxemia in 18 per cent of all deaths. No pathology was found at the autopsy in 55 per cent of these fetuses and infants. These are the babies that should be saved.

Peckham noted a close correlation between the fetal mortality and the height of both systolic and diastolic blood pressure. The fetal mortality was 9 per cent with a systolic pressure less than 149; 11 per cent for 150 to 179; 19 per cent for 180 to 209; and 42 per cent for 210 or more. He also noted that the fetal mortality was 8 per cent with no albuminuria; 10 per cent with 1.9 gm. per cent; 23 per cent with 2 to 4.9 gm. per cent; and 42 per cent with 5 gm. per cent and over.

The fetal and neonatal mortality depends on the severity of the toxemia, the age of the fetus when born, and the type of delivery. Our data for 1936 to 1938 demonstrate a marked reduction in both fetal and maternal mortality. The procedures used are discussed in the following paragraphs.

Clifford reports that if the mother's systolic pressure is 180 or more, 50 per cent of the babies are stillborn. They attempt to prolong the pregnancy of toxemic patients until the fetus weighs at least four pounds, but as soon as the blood pressure reaches the above level and the fetus is estimated to weigh four pounds, the pregnancy is terminated. They believe that the mother delivered of a live four-pound baby will have a greater chance of having a baby to take home with her than she would if they waited for a larger sized baby only to have it delivered stillborn.

Over 60 per cent of the fetal and neonatal mortality in toxemic patients occurred in the fetuses weighing 1,000 to 2,000 gm. Since maternal toxemia has no further effect on the fetus once it is born, the treatment of the mother should be directed to prolonging the pregnancy as long as compatible with her best interests to obtain as old and as heavy a baby as possible. The method of delivery with the lowest mortality should be selected. The age of the fetus is of more importance than its weight. The babies, if born prematurely, are usually more vigorous than their weight would warrant.

Clifford reports that the premature mortality at the Boston Lying-in Hospital was 55 per cent for breech delivery, 54 per cent for cesarean section, 33 per cent for normal vertex, and 15 per cent for low forceps with episiotomy. He ascribes the high mortality in premature babies to the use of analgesic drugs during labor and prolonged anesthesia during delivery. The low mortality for the last group he attributed to the shortening of the second stage by an episiotomy and use of forceps with a resultant reduction of trauma to the head. He notes that if no preoperative medication is used in cesarean section and if this is done under local anesthesia or a very rapid extraction is performed under short gas

anesthesia, the infant usually breathes and cries spontaneously, in contrast with their previous experience of deeply asphyxiated babies which were difficult, if not impossible, to resuscitate.

The stillbirth and neonatal mortality for all cesarean section fetuses weighing over 1,000 gm. is 7.9 per cent. The section mortality of term babies is 3.3 per cent (neonatal 2 per cent) and of premature babies 4.6 per cent (neonatal 3.3 per cent). The mortality for viable fetuses from toxemic patients delivered by section is 12 per cent which is excessively high. Since the operation is usually performed in the interest of the baby, this high mortality deserves comment. Half of the deaths are in the prematures and yet Potter has found no pathology in a high percentage of these babies with the exception that she has noted that the amount of fluid in and over the meninges is increased.

Robb reports a fetal mortality of 41 per cent for premature infants delivered by cesarean section and suggests the following explanation. The usual technique of extraction of the fetus is rapid and the cord is clamped at once. Thus, the uterus has not been able to squeeze most of the placental blood into the fetus resulting in a loss of blood which may be excessive in premature fetuses. In view of Potter's finding of cerebral edema, we believe that the loss of plasma protein is also of importance. No studies have been made of these fetuses. Barcroft reports that at a period in the goat which corresponds to about thirty weeks in the human gestation, approximately 75 per cent of the blood is in the placenta, while only 25 per cent is in the placenta at term. Thus, the improper delivery of the premature baby would leave a large amount of fetal blood in the placenta. The treatment used by us is to deliver the head of the fetus and produce uterine contractions with an oxytocic and when the uterus contracts, to deliver the body slowly. When the cord has stopped pulsating, its contents are stripped toward the fetus. No drugs are given before operation and over 60 per cent of our cesarean sections are performed with local anesthesia. As soon as the cord is dressed, the premature baby is placed in a Hess incubator.

Since we strive to decrease the fetal mortality in pregnancy toxemia, the question naturally arises as to the future of these babies. No data are available for term infants, but Mohr and Barthelme have made an exhaustive study of 250 of the 987 prematurely born children treated at the Sara Morris Hospital Premature Station. The controls were 152 siblings. They state that from ages one year to seven years inclusive, a sufficient number of examinations have been made to insure reliable conclusions. The physical growth, mental development, habit formation, and social adaptation were analyzed. If those babies having intracranial hemorrhage are omitted, the development of the premature baby from a toxemic mother is similar to that of other prematures and what is most important, similar to that of term babies born of normal mothers. Therefore, if the fetus is born alive and survives, maternal toxemia can have no further influence on its life or development.

Young has reported that the incidence of abortion, premature delivery, stillbirth, and abruptio placentae is 23 per cent in patients who have had toxemia of pregnancy and 10 per cent in normal patients. Our data

indicate that 25 per cent of the pregnancies after eclampsia and 15 per cent after nonconvulsive toxemia terminate as described above. Thus, the patient with toxemia is not only confronted with the possibility of her own death or of permanent vascular-renal damage but her chance of leaving the hospital with a live baby is far less than that of the normal pregnant patient.

The fact that there have been no maternal deaths due to nonconvulsive toxemia since 1932 can be attributed to a more thorough study of every patient, earlier hospitalization, and better preparation for delivery. Intravenous injections of glucose solution, dietary regime, blood transfusions, the use of sedatives, diuretics, etc., have their place in decreasing maternal mortality. Since the premature mortality decreased with advancing age at birth, these various procedures have also reduced the fetal mortality because each additional week of intrauterine life increases the fetal weight and age.

Classifying patients as to degree of severity is always questionable and the tendency after discharge is to minimize the seriousness. However, using criteria previously described we divided our cases as follows:

	MILD	MODERATE	SEVERE	TOTAL
	%	%	%	%
Pre-eclampsia	25.7	15.0	6.7	47.4
Essential hypertension	6.2	3.4	2.4	12.0
Vascular-renal disease	12.5	11.3	12.0	35.8

Over 70 per cent of the patients with nonconvulsive toxemia have only a moderate blood pressure, a small amount of albumin, variable amounts of edema, and no symptoms of headache, dizziness, etc. In other words they are mild cases and although they may become severe, treatment will not influence maternal or fetal mortality unless it is basically sound and includes such items as rest, proper food intake, and especially elimination. This preponderance of patients with mild toxemia explains, in great part, the excellent results attributed by various investigators to a high protein intake, the regulation of water balance, a high vitamin intake, etc. We believe that if a result is to be ascribed to a specific substance or procedure no other type of treatment must be used than the one in question.

The serum protein level of our patients is not in the edema level. The average for the normal pregnant patient is 6.5 gm. per cent, and for the toxemic patient, 6.0 gm. per cent. Furthermore, Dieckmann states that the determined and calculated serum colloid osmotic pressure is within normal limits in the normal pregnant and toxemic patients studied by him and that some other theory must be used to account for the edema. The attempt to feed these patients high protein diets has been unsuccessful because we could not, as a rule, force the patient to take more than 100 gm. per day. Nonprotein nitrogen determinations made on twenty-four-hour urines from patients living at home indicate that they ingest on an average of 60 to 80 gm. of protein per day. Thus, the majority of our patients have an adequate nitrogen intake.

If albumin is found during the prenatal examination, the patient is instructed to save the urine for twenty-four hours, measure it, and bring a

sample of the mixed twenty-four-hour specimen. The amount of protein is determined by the Esbach method. If there are more than 5 gm. per twenty-four hours the patient is hospitalized. If the patients show edema, gain more than one pound per week, or have a blood pressure of more than 140 systolic, they are placed on a salt poor diet. The twenty-four-hour excretion of sodium chloride must not exceed 3 gm. if the limitation is to be of any value. If the weight gain is still excessive, fats are either curtailed or eliminated from the diet. An unbalanced diet is not used for a period longer than two weeks before delivery is contemplated, and the eclamptic diet which consists of fruits and fruit juices is used for only one week.

The average weight gain according to numerous reports in the literature and our own data is 21 pounds. We believe this is excessive. If at conception the patient's weight is normal, all available data indicate that there is no need for the normal pregnant patient to gain more than the weight of the products of conception and of the physiologic changes associated with pregnancy. The weight of the fetus is comparatively negligible until the last trimester of pregnancy when its weight increases from 1,000 gm. at twenty-eight weeks to 3,400 gm. at term. During this period its requirements for calcium, phosphorus, nitrogen, and iron are maximum. This indicates that the patient's diet for the first six months of pregnancy should be no different from that of the nonpregnant. It may be that the low incidence of toxemia among some native peoples is due to this fact. We have been attempting to obtain data as to weight gains in animals during pregnancy, but here again conditions are artificial and all domestic animals gain weight during pregnancy. Roderick and Harshfield have studied a pregnancy disease of sheep and state that the disease has a mortality of 90 per cent and that 10 to 25 per cent of a flock will die. Important factors are overfeeding and lack of exercise. If the sheep are compelled to walk several blocks for their food, the disease does not occur.

It has been known for many years that patients who have marked albuminuria or marked hypertension usually have very small babies and small placentas. It has always been assumed that the size of the fetus is due to the small placenta. We have noted on a number of occasions that the babies of patients who had been treated for hyperemesis gravidarum with large amounts of intravenous glucose were larger than normal. Furthermore, the babies born of diabetic mothers whose blood sugar level was always high are usually overweight. It seemed that if the fetus had an excess of easily available food (glucose) during the first trimester, it would be larger and thus require a larger placenta. It is highly probable that the size of the early placenta is controlled by the fetus and not vice versa. We have given intravenous injections of 500 c.c. of a 20 per cent glucose solution to a few patients with vascular-renal disease, but in none of them before the middle of pregnancy. We have also suggested to several of these patients when seen early in pregnancy that they attempt to maintain a high blood sugar by constantly eating candy. On several occasions living babies have been obtained in these patients with vascular-renal disease where previously they had had one to three

stillborn fetuses. We have also been giving these patients 1 to 2 gr. of thyroid per day with the idea of stimulating their metabolism. To date we have seen no ill effects. Our series is too small to warrant any conclusions as to the value of thyroid therapy.

Shute stated that he could stop further separation of the placenta in early cases of abruptio placentae with fresh wheat germ oil. Since this condition occurs frequently in patients with vascular-renal disease, we have been giving such patients vitamin E after the twenty-fourth week. We rarely expect to carry these patients beyond thirty-two to thirty-four weeks because either the blood pressure goes to 200 systolic or more or the albuminuria exceeds 5 gm. per twenty-four hours. In either event we believe the pregnancy should be terminated in the interest of the baby. Shute now states that his results are due to the use of fresh crude wheat germ oil which has been kept cold.

Any increase in the severity of the signs or appearance of the usual premonitory symptoms in the *pre-eclamptic* patient should always suggest that eclampsia may be imminent. Thus, admission to the hospital is imperative and termination of the pregnancy advisable if the systolic pressure reaches 170 or if it increases 50 mm. or more; the urine volume decreases to less than 800 c.c. per twenty-four hours; the albuminuria amounts to more than 5 gm. per twenty-four hours or its concentration is 0.5 per cent; the weight gain has been more than 1.5 pound per week with a sudden increment of two or more pounds per week; the edema becomes marked or if cerebral or visual symptoms appear.

If the patient has *essential hypertension* or *vascular-renal disease,* eclampsia is uncommon, but the danger, especially after thirty weeks, is fetal death in utero because of placental infarction, retroplacental hematoma, or abruptio placentae. These patients are hospitalized and the pregnancy terminated when the systolic blood pressure rises to 190 mm. or more; albuminuria is more than 5 gm. per twenty-four hours; marked edema appears; or the previously described symptoms develop.

Pregnancy is either the cause of the toxemia or a very important exciting factor, and for that reason it must occasionally be terminated. It is the consensus of opinion today that the majority of the toxemias of pregnancy are best treated by medical means until it is possible to terminate the pregnancy by a safe induction of labor. The following outline lists the criteria used for determining the management of the pregnancy. Each case must be individualized. The age, parity, duration of the pregnancy, fertility of the patient (number of years married and time required to conceive), advisability of future pregnancies, and the diagnosis of the condition, i.e., whether it is pre-eclampsia or vascular-renal disease, must be carefully evaluated.

The patient with chronic glomerulonephritis as a rule cannot go through a pregnancy without danger to life and has very little chance of obtaining a living baby. The patient with vascular-renal disease will usually have more evidence of increased damage as indicated by a higher blood pressure, decreased renal function or increased retinal pathology if the pregnancy is permitted to continue.

CRITERIA USED FOR DETERMINING THE MANAGEMENT OF THE PREGNANCY

Group A

1. The systolic blood pressure is consistently 160 or more.
2. The albuminuria amounts to more than 5 gm. per day.
3. There is edema of the legs, hands, face, and/or of the vulva.

Group B

4. Cerebral, visual, and gastrointestinal symptoms and signs.
5. Hematuria.
6. Oliguria or anuria.
7. Jaundice.
8. Tachycardia of 120 or more per minute.
9. Cardiovascular impairment (edema of the lungs, cyanosis, etc.).
10. Blood nonprotein nitrogen which is more than 50 mg. per cent.
11. Blood concentration as indicated by abnormally high or increasing hemoglobin, cell volume, serum protein concentration, or specific gravity of the blood.

PREGNANCY

Before 26 weeks: Terminate if more than one of the signs of Group A are present or if there is no appreciable improvement after 7 days of adequate treatment or if any of Group B are present.

27-31 weeks: No interference before thirty-two weeks' gestation unless one or more of Group B signs develop or those in A increase in degree despite treatment.

32-40 weeks: If Group B signs are absent, medical treatment until the cervix is soft and effaced and a medical or mechanical induction of labor will be successful. If Group A signs increase in degree or if any of B appear, the pregnancy should be terminated either by:

1. Rupture of the membranes and/or insertion of a bag, or
2. Cesarean section if the cervix is uneffaced and firm. The environment must be suitable and local anesthesia should be used.

Many obstetricians are of the opinion that the amount of vascular-renal damage parallels the duration of the disease and, therefore, advocate the early termination of pregnancy. Gibberd states, "If a patient with albuminuria is treated carefully over a long period, and induction of labor is performed just soon enough to avoid eclampsia, there is a tendency to regard such treatment as an obstetric triumph made possible by the great clinical acumen of the obstetrician. Actually, it is often a grave obstetric blunder, in that, as a result of the prolonged albuminuria, an incurable chronic nephritis may develop." He, therefore, advises that termination of pregnancy be seriously considered if the albuminuria persists for three weeks. We have recently reported our findings in a group of 340 patients who had two or more pregnancies, the first of which was complicated with toxemia. It is our belief that true eclampsia and pre-eclampsia, irrespective of duration, cause no permanent vascular or renal damage. That if the hypertension, proteinuria, or impaired renal function is still present six months or more post partum or if toxemia recurs in a subsequent pregnancy, the patient has an essential hypertension or vascular-renal disease. These diseases differ only in degree. We believe that the patient either had hypertensive arterial disease before pregnancy or a predisposition to it by inheritance or by physical or mental instability (as in the nervous and high strung) and the pregnancy is the exciting factor. Thus, while our ideas as to etiology differ from those of Gibberd and other obstetricians, yet our treatment is in general in accord with that usually prescribed.

CONCLUSIONS

The average maternal mortality in representative hospitals for nonconvulsive toxemia of pregnancy is 1.7 per cent. Our mortality for preventable deaths is 0.4 per cent. One-half of our immediate deaths were due to infection and the remainder to heart disease and/or anemia.

Over 13 per cent of our toxemic mothers are discharged without a living baby. Seventy per cent of these deaths occurred in fetuses weighing less than 2,500 gm., but this group comprised only 20 per cent of the series. The fetal mortality for all fetuses weighing over 1,000 gm. was 8.0 per cent; over 1,500 gm., 6 per cent; and over 2,500 gm., 3.9 per cent. Toxemia does cause an increased fetal mortality.

Cesarean section yielded the lowest mortality for fetuses weighing from 1,000 to 1,999 gm. (31 per cent) and over 4,000 gm. (0 per cent). The mortality for viable fetuses was 12.0 per cent.

Normal labor gave the lowest mortality for fetuses weighing 2,000 to 3,999 gm. (3.0 per cent). The mortality for viable fetuses was 5.2 per cent.

Induction of labor gave a high mortality for all weight groups and is now used only in selected cases.

The fetal and neonatal mortality for the first five years was 15.5 per cent and for the last two years has been 7.2 per cent. Similarly the mortality for fetuses weighing over 1,500 gm. was 6.8 per cent for the first period and only 2.3 for the last two years.

Labor should only be induced in suitable cases. That is, there should be no cephalopelvic disproportion, the fetal position should be a normal one, and the cervix should be "ripe" (effaced, soft, and dilatable). Rupture of the membranes and, if contractions have not started at the end of twelve hours, the injection of one or two minims of pitocin at thirty-minute intervals until uterine contractions occur every three or four minutes or until 8 doses have been given is the safest method. Occasionally when rapid delivery seems imperative, a bag may be inserted within the uterus.

Cesarean section should only be used in the pre-eclamptic patient when eclampsia seems imminent and delivery through the vagina seems unwise. It is also indicated in patients with essential hypertension or vascular-renal disease in the interest of the baby if delivery is necessary before term and the cervix is not "ripe." Sterilization as an indication for the operation is unwarranted.

The morbidity for all patients amounts to 7.8 per cent, but for toxemic patients alone, the morbidity is 32 per cent. This high incidence of fever is due primarily to the excessive vaginal manipulation and high operative rate in toxemic patients.

The duration of labor in toxemic patients is longer than normal.

The weight gain in normal pregnancy should amount to the weight of the products of conception and of the physiologic changes associated with pregnancy.

The weight of the fetuses from toxemic patients is as a rule less than the average for the period of pregnancy. These babies are immature

rather than premature and are usually much more vigorous than their weight warrants. A high carbohydrate diet during early pregnancy may be of value in producing a larger fetus in patients with vascular-renal disease.

No drugs which depress the respiratory center, such as morphine, hyoscine, ether, paraldehyde, etc., should be used before delivery if the pregnancy is being terminated prematurely. Magnesium sulphate or sodium luminal may be given intramuscularly if convulsions seem imminent. Analgesia may be obtained with intermittent gas anesthesia. Episiotomy is especially indicated in the delivery of the premature baby.

The obstetric management of toxemic patients, meaning the proper use of medical and surgical treatment, results in a lower maternal and fetal mortality. Each case must be individualized.

Prenatal care should be intelligently administered in that abnormalities of weight, blood pressure, and urine must not only be recognized but their importance appreciated and proper treatment instituted. We cannot prevent mild toxemia but the rate of development of severe preeclampsia can be retarded and the occurrence of eclampsia forestalled. Treatment must be begun early and if necessary the pregnancy terminated before cerebral and visual symptoms appear, or if the patient has vascular-renal disease, before additional injury to the maternal kidneys and arteries has occurred or the fetus dies in utero.

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DISCUSSION

DR. DAVID A. HORNER.—About twelve years ago, Hillis, Lash, Cornell, Fitzgerald and I started a study on the therapy of the convulsive type of toxemia at the Cook County Hospital. We prescribed therapy in such a way that we could compare the various treatments. A suggestion to Dieckmann and Brown would be that they use a similar method in their own service perhaps even to the extent of selecting alternate cases, every other one being kept for control purposes with no special treatment other than the simple salt-free diet and routine of hospitalization.

While Dieckmann gives us nothing new in the line of therapy, we find that the baby appears to be given more importance than heretofore. In my own work, I have felt that carrying a mother until viability of the baby or further toward term was dangerous to her own life. Even though she and her baby survived the im-

mediate toxemia, would she live long enough to raise that child because of the added damage to herself that we permitted in the waiting? The damage to her hepatic, renal, and vascular systems is even greater if she must undergo the strain of an induced labor. I have lost too many babies by medical or bag induction and hence cesarean section under local anesthesia at the earliest moment consistent with the safety of mother and baby would be my choice in those patients presenting alarming symptoms. I believe also that the sooner an unborn baby is separated from the influence of its toxemic mother, the better its chance for life, no matter how premature, and conversely, the longer it is attached to its toxemic mother the less it is likely to survive even by the method which gives it the best chance for life, viz., cesarean section.

DR. EDWARD ALLEN.—I have analyzed the toxemia cases we have had on the service at the Presbyterian Hospital. Out of 5,722 deliveries there were 357 toxemias of pregnancy. There were 27 fetal deaths; this is an uncorrected fetal mortality. Labors were induced by various methods, some similar to and some different from Dieckmann's. There were 28 cesarean sections which accounted for one fetal and one maternal death. In 32 patients labor was induced by castor oil and quinine aided by separation of the membranes. There were six fetal deaths in this group. Forty-seven of the patients were delivered by castor oil, quinine and bag induction, accounting for seven fetal deaths. Forty-one went into labor after rupture of the membranes which occurred spontaneously in most instances and which probably accounts for the low fetal mortality. Only one infant succumbed in this group. There were 12 therapeutic abortions for toxemia and 13 cases of convulsive toxemia. The uncorrected fetal death rate in our series, therefore, was 7.3 per cent.

I would like to ask Dr. Dieckmann whether he had any tetanic contractions of the uterus following artificial rupture of the membranes and injection of pitocin. We have avoided the use of these oxytocic drugs in the induction of labor, mainly, I think, because in a teaching hospital we have felt that students are a little likely to carry any method we use a little farther than the absolute indications might warrant.

We have not used as a partial indication for cesarean section the need for sterilization as frequently as Dr. Dieckmann has suggested. Neither have we been quite so certain in the early allocation of these patients to their toxemic type. We have been more in favor of sterilization by the vaginal route later in the puerperium when we have additional evidence of the type of toxemia.

DR. DAVID S. HILLIS.—There are two things with regard to the management of a toxemia of pregnancy which must be kept in mind. The first is that every woman with a blood pressure of 140/90 deserves our most careful and accurate attention. An increase to this figure or the appearance of other symptoms, is an indication for hospitalization. It is our opinion that throughout the country the death rate from toxemias is increased because the general practitioner waits for the patient to have some severe symptom or a much elevated blood pressure.

The second point is that it is impossible to decide in an individual case of toxemia hypertension whether or not the patient will have convulsions. A patient may have convulsions with a blood pressure of 140/80. Of course this is not common, but others are frequently admitted to the hospital who have had no convulsions and the blood pressure is found to be 200/140.

DR. JOSEPH B. DELEE.—I will discuss three points. First, I would like to define here again as I have done repeatedly for many years the prophylactic forceps. The prophylactic forceps operation is intended to fulfill two general indications or rather two sets of indications. It is intended to be used when the head of the fetus, in normal labor, comes down to the pelvic floor and just begins to separate the pillars of the levator ani. Then prophylactic forceps is done to avoid two sets of dangers, one for the mother and one for the baby. The set for the mother consists of the prevention of injury to the pelvic floor, the connective tissues, the muscles, the displacement of the rectum and pushing back of the anus, and particularly, the prevention of cystocele. It also prevents the tearing out of the cervix, its dislocation from

the bed of connective tissue. As far as the baby is concerned, it prevents congestion of the brain, anoxemia, which all students of the subject have proved is the cause of cerebral hemorrhage, and disturbances of the brain which show up during later life. I do not think there can be any objection to the use of prophylactic forceps in this manner.

The second point is that Dr. Dieckmann did not mention bleeding. I believe bleeding still has an occasional use in eclampsia, especially when convulsions are occurring in great rapidity, and defy the routine treatment. Sometimes even if the pulse is not high or the blood pressure not high it may be useful. Just recently we had a patient at the Lying-in Hospital in which the convulsions were coming every hour almost on the hour. We withdrew 300 c.c. of blood and within an hour and a half she sat up in bed and answered questions. She had only one more convulsion.

One other point: On September 6, I was in Berlin and had a long talk with Professor Stoeckel about eclampsia. He is one of the proponents of immediate delivery. When notified that a women with fits is on the way to the hospital, he calls his operating room and by the time the ambulance is there he is ready to deliver the woman. On the other hand, at the Charité Hospital the opposite is true. There they carry out conservative treatment. Stoeckel said he was at the meeting in Amsterdam of the International Congress of Obstetricians and Gynecologists where they were about evenly divided on the question of conservatism. I have not read the reports from Amsterdam. Our experience is against cesarean section and rapid delivery. Medical treatment of eclampsia is best.

DR. DIECKMANN (closing).—In reply to Dr. Hillis, I may say the purpose of our paper is to stress the early treatment of toxemia of pregnancy. I believe if one is following these patients himself that he can, with a fair degree of accuracy, make a correct diagnosis as to the type of toxemia. The results as published in this, as well as other papers by us, indicate that the maternal and fetal morbidity and mortality have been better within the past few years as compared to the first period.

We have stressed in our paper that we do not favor the terms conservative and radical. Our operative incidence is still quite high but I believe our results of the past few years indicate a low maternal and fetal mortality. I believe a conservative treatment with a patient showing increasing damage is really radical. Likewise, to immediately terminate the pregnancy in a mild case of pre-eclampsia is radical. I think the obstetric management should be a wise combination of the medical and surgical treatment.

Weinstein and Wickerham: Yeastlike Fungi of the Human Vagina. Yale J. Biol. & Med. **10:** 553, 1938.

In a study of vaginal secretions of 375 women it was found that 23.3 per cent of the pregnant and 7.3 per cent of nonpregnant women harbored yeastlike organisms; that is, 64 per cent of the nonpregnant group and 56 per cent of the pregnant showed signs of infection of the vagina by these organisms. The absence of noticeable disease of the vagina when yeastlike fungi are present is not necessarily an indication of the nonpathogenicity of the organism but may indicate a resistance on the part of the host. There seems to be strong evidence for the existence of a carrier state with the yeastlike fungi. Studies of the vaginal flora in cases in which yeastlike fungi were present revealed that the Döderlein bacillus can be recovered with great frequency, thus casting doubt on the inference that this organism is an indicator of vaginal health. *Staphylococcus aureus* and *albus*, hemolytic and nonhemolytic streptococci and *Escherichia coli* were also recovered.

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THE PHYSIOLOGY OF HYPERTENSION IN ECLAMPSIA

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DURING normal pregnancy there are many circulatory adjustments, and it is remarkable that the maternal blood pressure should maintain its normal level in spite of significant changes of blood volume, blood viscosity, and cardiac output. Sustained arterial hypertension occurs, however, in about 9 per cent of late pregnancies.* Among this group are recognizable cases of chronic nephritis, essential hypertension, and other hypertensive diseases encountered in nonpregnant individuals. The majority of patients with hypertension, however, belong in the groups known as pre-eclampsia and eclampsia, and it is only with this syndrome that we are concerned in the present discussion. It is extremely uncommon to find a true toxemia of late pregnancy without hypertension. An elevated blood pressure is, in fact, the cardinal and most constant sign, and yet its mechanism has never been satisfactorily elucidated.

It would seem worth while to evaluate the several factors which might be the immediate cause of the hypertension, and to consider particularly the possibility that the hypertension of pregnancy toxemias may be due to the liberation of a pressor substance from the maternal kidney or the placenta.

From the standpoint of hemodynamics, the immediate cause of any rise in the blood pressure must be attributed to one or more of five factors:[1] an increase in the cardiac output, an increase in the ratio of the total blood volume to the capacity of the vascular bed, an increase in the viscosity of the blood, a decrease in the distensibility of the arteries, or an increase of the peripheral resistance.

In pregnancy the dynamics of the whole circulatory system are disturbed by a variety of factors. For instance, the increase in the vascular system of the uterus might act as a low resistance arteriovenous shunt which would tend to lower the total peripheral resistance. That such a shunting effect takes place is suggested by Barcroft's[2] observations on the high oxygen content of the uterine veins during the first half of pregnancy. The similarities between the circulatory changes of pregnancy and those accompanying arteriovenous fistula have been pointed out by Burwell.[3] Such a low resistance shunt would tend to lower the diastolic pressure and increase the pulse pressure. On the other hand, the additional capacity of the circulatory system due to the increase in

*Hospital incidence: 346 women out of 3,850 consecutive deliveries at the Los Angeles County Hospital maintained a blood pressure at rest exceeding 140 systolic and 90 diastolic.

the vascular bed of the gravid uterus would tend to slow the circulation while the simultaneous increase in the volume of blood would tend to accelerate it. Similarly the decrease in blood viscosity must tend to lower the blood pressure.

Thus we have a variety of contrary phenomena whose existence is almost beyond doubt but the relative magnitudes of whose effects have not been measured adequately. It is significant, however, that the vast majority of women (over 90 per cent) compensate so smoothly for these changes that the resulting alterations in arterial pressure, venous pressure, and pulse rate are below the limits of significance. Undoubtedly the compensatory mechanisms of the vasomotor system are called into play in the redistribution of blood, and vasoconstrictor influences in certain areas of the body may be acting to compensate for the lowered resistance of the gravid uterus. This is suggested by the observation of Kyrieleis and Schroeder[4] that normal pregnancy is accompanied by a narrowing of the retinal arterioles, and also by the finding of decreased capillary flow in the nail beds of most pregnant women.[5] Extensive confirmation of these two findings is therefore desirable.

Cardiac Output.—It is generally agreed[6] that the cardiac output during the latter half of normal pregnancy is substantially increased, but no measurements have been found on toxemic patients. Such an increase in circumstances other than pregnancy would be reflected in an increase in the product of pulse rate and pulse pressure. That such pulse rate and pulse pressure changes are not regularly found in pregnancy indicates that the observed rise in cardiac output is closely balanced by one or more of several factors: (1) diminished blood viscosity, (2) an increased distensibility of the arterial tree, (3) an increase in the capacity of the uterine arterial system, or (4) a lowered resistance due to the increased cross-sectional area of the uterine blood vessels. Since increased cardiac output in man is almost invariably associated with a normal or lowered diastolic pressure, the rise of diastolic pressure in eclampsia indicates that a further augmentation of the cardiac output is not the immediate cause of the hypertension in this disease.

Blood Viscosity and Blood Volume.—The effective viscosity of the blood varies with the blood pressure and the diameter of the smaller blood vessels[7] and, therefore, has not been measured in man. The in vitro viscosity of the blood, however, varies roughly with the concentration of the red blood cells. Changes in the blood volume or in the specific gravity are rarely, if ever, the cause of sustained hypertension. In polycythemia vera, where both factors may undergo a marked increase, the blood pressure usually maintains its normal levels.[8] In normal pregnancy there is a hydremia often resulting in a 10 per cent increase in the blood volume,[9] and in pre-eclampsia this change is exaggerated,[10] but inasmuch as the increased volume is always accompanied by a blood dilution, the viscosity is decreased. The effect of the one change upon the blood pressure would therefore tend to counteract the effect of the other. This same reciprocal action would also hold true during the acute stage of eclampsia when, as Dieckmann[10] has shown, there may be a rather sudden concentration of the blood.

Such factors would hardly need to be discussed in detail were it not for the fact that some authors have attributed the hypertension of eclampsia to water retention, or even to the altered blood viscosity. The fact that the hypertension may subside after the establishment of a normal water balance is no proof that water or salt retention alone may be the cause of eclamptic hypertension. The occurrence of a positive water balance and the development of edema do not always result in an elevated blood pressure. Indeed, the most severe cases of eclampsia often have no clinical edema.

Blood pressure measurements on women with eclampsia, made at two-minute intervals during and after the rapid intravenous infusion of glucose-saline (1,000 c.c.) and blood or gum-saline (500 c.c.), show rises which rarely exceed 10 mm. Hg and are only transient. Similarly, the duration and magnitude of the fall of blood pressure following the withdrawal of 500 c.c. of blood during eclampsia are small. Since the spontaneous changes of volume and viscosity in the toxemias are of the some order of magnitude as these induced changes, the observations indicate that neither factor is of any considerable importance in the production of the sustained hypertension.

Distensibility of the Arterial Tree.—The only really satisfactory method of determining variations in this factor appears to be by measurements of pulse wave velocity. It has been demonstrated theoretically and experimentally, and confirmed by observations, that there is a roughly linear relationship between pulse wave velocity and arterial blood pressure.[11, 12] We find no reports of investigations designed to tell if this relationship is disturbed in the toxemias of pregnancy. On the other hand, histologic study fails to show organic changes in the muscular coat of vessels during eclampsia; nor is there evidence for any changes in distensibility other than the functional decrease which is the regular accompaniment of a raised diastolic pressure.*

Peripheral Resistance.—No satisfactory measurements of peripheral resistance in pregnant women have been published;[13] nevertheless, we are left with the conclusion that an increased peripheral resistance is the immediate cause of the elevated blood pressure. In this respect the hypertension of pregnancy toxemias is of the same immediate mechanism as that of chronic nephritis and essential hypertension.

That the changes in this resistance are functional rather than organic is suggested by the marked lability of the blood pressure, by the absence of histologic changes in the arteries and by the rapid subsidence of the hypertension in most instances after delivery. This suggestion is further confirmed by experiments in which the administration of sodium nitrite by mouth to a group of women with toxemias of late pregnancy resulted in a greater fall of the blood pressure than that observed in normal pregnancies.[14]

Landis,[15] Ellis and Weiss[16] and others have repeatedly shown that in normal persons and patients with hypertension the bulk of the peripheral resistance is in the arterioles rather than the capillaries, and it is reasonable to consider whether the

*Such a decreased distensibility resulting from the raised diastolic pressure in eclampsia might well account for the increased pulse pressure observed in that disease.

same may hold true for the hypertension of pregnancy toxemias. An attempt in four cases of eclampsia to confirm the findings of Nevermann[5] regarding capillary spasm—as indicated by a cessation of flow—was unsuccessful in that these four patients showed no recognizable differences from ten male interns with respect to blood flow or morphology of the capillaries of their nail beds. A prolonged stopping of capillary blood flow, rather than being due to capillary "spasm," is in fact more commonly due to arteriolar constriction.

While studies of the capillary pressure[17] have shown high readings in some cases of more severe eclampsia, this sheds no light on the question of the resistance offered by the capillaries. Owing to our lack of information on this point it is difficult to eliminate the capillary bed as the source of the raised resistance, although from both a physiologic and anatomic standpoint the arterioles are the probable structures responsible. Indeed, Wagener[18] and a number of others have actually observed the diminished diameter of the retinal arteries in the toxemias of late pregnancy.

Since it seems very likely that the proximate cause of the hypertension of eclamptogenic toxemias is a diffuse functional arteriolar constriction, it is necessary to consider the known causes of increased arterial tonus.

The direct effect of temperature changes upon arterial tonus[19, 20] may be eliminated from our consideration. It would seem that for such a phenomenon to become sufficiently generalized to alter the blood pressure measurably, the temperature of the whole body would need to be reduced far below the usual clinical limits.

There remain two causes of vasoconstriction—vasomotor changes and direct chemical excitation of the arteriolar muscle. The decision as to which of these two factors plays the predominant role is one of the important unsolved problems remaining in the study of eclampsia.

Before discussing the question of nervous versus chemical influences, it is necessary to divert attention to the anatomic findings in the eclamptogenic toxemias.

A Circulating Vascular Toxin.—It has been repeatedly noted that the most constant and probably the most significant lesions of eclampsia are vascular in nature.[21] Even the mild grades of pre-eclamptic toxemias may show glomerular changes when connective tissue stains are used, and there is evidence that such capillary injury is often of a permanent nature.[22] Damage to retinal vessels may be readily demonstrated.[18] The smaller blood vessels of the placenta[23] and of the liver[24] show similar changes. It is quite possible that such vascular injury may give rise to the multiple small thromboses, to the edema of all organs and to the visceral hemorrhages which so commonly accompany eclampsia. Such vascular lesions bear little relation to the degree or the duration of the hypertension; they are not, therefore, secondary to the hypertension, nor necessarily comparable to the vascular lesions observed in experimental malignant hypertension.[25] The only postulate which is tenable is the age-old concept of a circulating "toxin." Whether this consists of the presence (or absence) of a chemical substance in the blood or a physical alteration of the blood is not known.

The remainder of our discussion is, therefore, based on the assumption that such a change in the blood of eclampsia does exist, and for the sake of convenience—realizing the dangers of applying any term to an unknown factor—we will refer to this as the "vascular toxin."

The Source of the Vascular Toxin.—The full syndrome of preeclampsia or eclampsia with the characteristic histologic lesions of the viscera is not observed in the male nor in the nonpregnant female; therefore it is obvious that the products of conception are in some way concerned with the production of this vascular damage. Such a statement is essentially a truism, and yet its full significance has been ignored by some investigators who either evade the question or state that pregnant women develop eclampsia because they "react differently" to such diseases as glomerulonephritis, essential hypertension, hyperpituitarism, hypothyroidism, hypercholesteremia, urinary back pressure, intestinal stasis, pyelonephritis, salt retention, abscessed teeth, and so on. Any one of these conditions might predispose to the development of eclampsia, but the mechanism of such an effect is at present unknown.

Several authors have ascribed eclampsia to the action of some metabolite of the fetus itself, or to the interaction of fetal and maternal blood. In a previous communication,[26] attention was called to the fact that the toxemias of late pregnancy are several times more common in cases of hydatidiform moles than in normal pregnancies, and it was suggested that this fact might be related to the volume and activity of chorionic tissue. Eclampsia itself has been reported many times with moles. Not only is the fetus eliminated as a source of the vasotoxic factor in such cases, but the placenta is definitely implicated.

The studies of Bartholomew and Calvin[27] and others seem to show beyond reasonable doubt that there is a positive correlation between placental infarcts and eclamptogenic toxemias, although the question whether such vascular changes are of primary or secondary importance has not been settled. The suggestion that autolytic products arising from these degenerative areas have both toxic and pressor activities is intriguing, but awaits proof. Such degenerative changes would undoubtedly reduce the secretory powers of a placenta, whereas the work of the Smiths[28] regarding the increased chorionic gonadotropic hormone content in toxemic placentas would seem to indicate an increased secretory function in eclampsia. In either case the placenta is further implicated, and it is most reasonable to postulate that placental activity is directly responsible for the development of toxic properties in the maternal blood.

At this point we may well inquire into the relationship which this toxic factor bears to the production of an increased peripheral resistance. There are four possibilities: (1) The vascular toxin may sensitize blood vessels to the action of normally present nervous or hormonal vasoconstrictor influences (e.g., sensitization to pitressin by estrogens); (2) it may synergize (i.e., activate or potentiate) the action of a normally present pressor substance (e.g., renin, postpituitary principle); (3) it may stimulate the production of increased nervous or chemical pressor activity by another organ (e.g., by initiating a renal hypertension); or (4) it may itself be a pressor substance. All such possibilities must be borne in mind during the course of investigations on the etiology of the toxemias of late pregnancy.

Vasomotor Influences.—Vasoconstrictor nerve impulses as a cause of the arteriolar spasm cannot be eliminated with any degree of certainty. The vasomotor centers are known to be directly and reflexly stimulated

by slight changes in the pH or in the carbon dioxide content of the blood, such as may occur in eclampsia. Reflex stimulation of the centers, such as occurs with pain, with the immersion of a hand into ice water (the "cold test"[29]) or even with psychic stimuli, may produce hypertension of varying degree in both normal and eclamptic patients. One may frequently observe, for example, the onset of convulsions and an abrupt rise of the blood pressure following a sensory or psychic stimulus to an eclamptic patient.

It must be remembered, however, that the presence of a chemical pressor substance does not necessarily preclude the superimposition of pressor or depressor effects by the nervous system, or vice versa. The problem, therefore, is the assessment of the relative importance of these two factors.

It has been repeatedly suggested that a hyperactivity of the vasomotor centers is associated with an increased sensitivity to the "cold test,"[29] or with an exaggerated rise of blood pressure under emotional stress,[30] or with a hypertensive personality make-up as found by Ayman[31] in his study of essential hypertension. The blood pressure responses of both normal and hypertensive pregnant women to the "cold test,"[32-34] and to a standardized emotional stimulus have been investigated.[14] (An analysis of our own data and a discussion of their interpretation is beyond the scope of this paper and will be presented in a separate note.) There appears to be a correlation between the degree of response to a sensory and a psychic stimulus, and though such responses seem to be exaggerated in those women who have essential hypertension in pregnancy, there is no significant difference between the responses of women with normal pregnancies and those with pre-eclampsia or eclampsia. The personality make-up of women with toxemias of late pregnancy has also been investigated[35] with similar conclusions.

These observations lend no support to the view that there is a hyperreactivity of the vasomotor centers in the toxemias of late pregnancy, although it must be pointed out that there is still no unanimity of opinion regarding the interpretation of such vascular reactions.

Pickering,[36] and Prinzmetal and Wilson[37] have evaluated the role of the vasomotor centers in essential hypertension by studying the changes of peripheral blood flow after nerve blocks which eliminate the vasomotor influences, and conclude that there is a humoral mechanism for the increased peripheral resistance. Similar studies have not been applied to the toxemias of late pregnancy. Bearing in mind the similarities between malignant hypertension and eclampsia, the possibility that the mechanism of the raised blood pressure in both these diseases, as well as in chronic nephritis, is similar, will be discussed presently.

Nervous Reflex from the Kidney.—In experimental oxalate nephritis[38] and in human acute nephritis,[39] the hypertension is allegedly due largely to a stimulation of the vasomotor centers through the afferent nerves of the kidney. Glomerular lesions of some degree almost invariably accompany the toxemias of late pregnancy, and in the mild grades of toxemias may be the only significant lesions demonstrable.[22] These changes are sometimes observed only after the use of special stains, but they may be

present even in the absence of albuminuria. The possibility that such renal changes may effect hypertension through the autonomic nervous system has not been excluded.

Pressor Substances.—Since there is not enough evidence to assign the hypertension of eclampsia to the nervous system, the remaining alternative explanation that a direct chemical excitation of the vessel walls is responsible for the increased peripheral resistance should now be considered.

The search for a pressor substance in the blood of eclamptic women has led to repeated failures. Metabolic products of the fetus or placenta, or autolytic products of placental infarcts have been incriminated without proof. Pressor tests of extracts or dialysates of eclamptic blood and spinal fluid on animals have led to negative results.[40] The hope raised by Anselmino and Hoffmann[41] by their alleged discovery of excessive postpituitary principle in the blood of patients with toxemias of pregnancy has been destroyed by the negative results of several workers.[42-46] Repeated and careful quantitative studies of the blood chemistry in the toxemias[47, 48] have failed to disclose the retention of any known substances in amounts sufficient to produce a hypertension.

Significant quantities of circulatory pressor substances might be demonstrable by the transfusion of adequate amounts of blood from toxemic patients to normal pregnant women. Such experiments in which amounts of 400 c.c. of blood were transfused failed to produce any increase of blood pressure in the recipients.[46] Are such failures to demonstrate a pressor substance in eclamptic blood sufficient proof of its nonexistence, or do they merely reflect the inadequacy of our methods?

A similar question is facing the investigators of experimental renal hypertension. The well-known experiments of Goldblatt and his associates[49] showing that a limitation of arterial blood supply to the kidneys results in permanent hypertension, was followed by demonstrations that such hypertension is not abolished by total sympathectomy, renal denervation, transplantation of the ischemic kidney or even pithing of an animal. The deduction was made, therefore, that the kidney, in response to the diminished blood supply, elaborates a pressor substance. A substance (renin) with marked pressor activity may, in fact, be extracted from renal cortex[50] and even subjected to quantitative assay.[50]

In spite of the fact that the presence of a circulating pressor substance in experimental hypertension is widely accepted, Collins and Hoffbauer[51] transferred large amounts of blood from dogs with renal hypertension to normal dogs without observing a rise of blood pressure in the recipients. Similarly, Pickering[52] and others have transfused normal human beings with blood from patients with malignant hypertension without observing a rise in blood pressure. By corollary, therefore, the failure to obtain a rise of blood pressure in human recipients of eclamptic blood does not eliminate the possibility of a circulating pressor substance.

More direct evidence for the existence of a circulating pressor substance is suggested by the report of Allen and Adson[53] of a woman who had a sympathectomy extensive enough to lower a previous hypertension

but who nevertheless developed later a transient hypertension in pregnancy. The interesting—though inadequately confirmed—observations of elevated blood pressures in the infants born of toxemic mothers[54] suggest the presence of a diffusible pressor substance in the maternal blood.

Pressor Substances from the Kidney.—At this point we are led to the consideration of certain hypotheses which await investigation.

It has already been mentioned that a vascular toxin originating in the placenta might cause sufficient renal injury to stimulate the vasoconstrictor centers through the renal afferent nerves.

Considering our discussion above, a more logical postulate is as follows:[22] The same factor producing the vascular damage and resulting in a thickened glomerular capillary wall results in a "throttling" of the blood supply to the entire kidney. In response to this lessened blood supply, the kidney elaborates a pressor substance which results in hypertension. In support of this theory is the recent work of Dill and Erickson[55] who have been able to produce a syndrome like that of human eclampsia by partially constricting the renal arteries of pregnant dogs and rabbits. The major objection to the theory is its failure to account for the differences observed between the effects of renal ischemia in gravid and nongravid animals or humans or to explain when and why such a reduction of the renal blood supply might occur.

The first objection—namely, the unexplained difference in the reactions of pregnant and nonpregnant animals—might be obviated if the placenta were capable of producing substances which potentiated the action of the renal pressor substance.

This leads us to the crucial question, in what circumstances might the placenta elaborate a potentiator of renin, a vascular toxin or even a pressor substance?

Pressor Substances from the Placenta.—It is well known that the blood supply to any organ is largely determined by its metabolic needs. Inasmuch as there are no nervous connections between the maternal organism and the placenta, the only means by which the latter could per se increase its supply of maternal blood would be by causing a maternal hypertension through a chemical mechanism. The possibility has been suggested[26] that the placenta elaborates such a factor in response to an inadequate blood supply, and it has been pointed out how this hypothesis may be correlated with known predisposing causes of eclampsia, such as primiparity, multiple pregnancy, hydramnios, hypoplastic genitalia and hydatidiform moles.

Which of these mechanisms accounts for the hypertension of the eclamptogenic toxemias awaits further investigation. We are not attempting to explain the entire etiology of eclampsia nor to advocate any single theory, but to point out certain physiologic facts and deductions which we hope may serve to clarify the pathologic physiology of the vascular system in the toxemias of late pregnancy.

SUMMARY

Changes in cardiac output, blood volume, blood viscosity or widespread organic arterial changes do not account for the hypertension

observed in the eclamptogenic toxemias. From a physiologic standpoint, the immediate cause of this hypertension is a functional and diffuse arteriolar constriction.

An increased activity of the vasomotor centers by direct or reflex stimulation cannot be eliminated as a cause of this increased peripheral resistance, but in eclampsia these centers are not abnormally sensitive to psychic or thermal stimuli.

The vascular pathology of eclampsia requires the postulate of a circulating factor which behaves as a vascular toxin. Chorionic tissue is probably responsible for this factor, and the stimulus for its production may be an inadequacy of maternal blood supply to the placenta.

This vascular toxin might produce hypertension in one of several ways: It may act directly as a pressor agent or accentuate the action of other known pressor agents. It is known to produce glomerular damage in the eclamptogenic toxemias. This renal damage may influence the vasomotor centers reflexly, or the resulting reduction of blood supply to the kidney may give rise to hypertension through the mechanism of renal ischemia. The available experimental evidence bearing on such hypotheses is discussed.

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MACROCYTIC ANEMIA OF PREGNANCY AND ANEMIA OF THE NEWBORN*

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THE relationship between anemia of the newborn and the hematologic picture in the mother has not been studied so extensively as have the anemias of these per se. In fact, the opinion is general that if such a relationship exists, it is only a slight one. Josephs[1] has stated, "We know very little of the factors regulating the formation and destruction of blood, and to what extent these processes in the fetus are influenced by factors derived from the mother. Probably not to any great extent, for anemia in the mother is only exceptionally attended by anemia in the newborn, and the makeup of fetal blood is so different from that of the mother that one must assume a largely independent mechanism." Anemia in the infant may depend upon an insufficient storage of iron in the liver or upon a deficiency of one or more extrinsic factors in the maternal diet.

There is a paucity of information on the relationship between macrocytic anemia of pregnancy and the blood picture of the newborn. A few divergent observations of infants' blood have been reported. If the infant comes to term the blood picture may be normal even though the mother has not received treatment during pregnancy.[2] It may be normal if the mother has been treated with antipernicious anemia principle, blood transfusion or vitamin B complex.[3] Apparently the status of the infant, both as to life and normality of its peripheral blood, depends mostly upon adequate treatment of the mother during pregnancy. One may infer that the factor producing macrocytic anemia in pregnancy may in some manner have a like effect on fetal hemopoiesis. The blood of the fetus has been shown to resemble the blood picture seen in pernicious anemia in response to effective antianemic principle.[4] The antianemic principle is supposedly derived by the interaction of an "extrinsic factor" in the diet and an "intrinsic factor" in the secretion of the stomach.

*Read (by invitation) at a meeting of the Obstetrical Society of Philadelphia, January 5, 1939.

Depending on the degree of deficiency of this principle, it may possibly be manifested in the blood picture of either the mother or infant, or both.[5]

Frequently there is found a reduction in gastric acidity during pregnancy, and this association with anemia is well recognized. Wintrobe et al.[5] have raised the question as to the presence of antianemic principle in the fetus and its possible relationship to anemia in the infant. As deficiency of the extrinsic factor can produce macrocytic anemia of pregnancy, with transfer of either little or none of this factor to the fetus, absence or diminution of intrinsic factor in the infant may be of considerable importance in producing or aggravating anemia in the newborn.

Because of the rarity of concomitant studies of the blood of newborn infants and their mothers suffering from macrocytic anemia of pregnancy, we are herewith reporting such a study.

Mrs. K., in 1930, when 18 years of age, had her first pregnancy which was normal except for ankle edema. During her second pregnancy she was admitted to Jefferson Hospital, in 1932, because of "low reserve kidney condition and high blood pressure." After three days, she signed her release and was delivered later at home on March 11, 1932, of a seven months' fetus, which died Aug. 11, 1932. The cause of death was ascribed to "enteritis (bacterial origin), lumbar abscess, bronchopneumonia and athrepsia." On Oct. 30, 1933, when six months pregnant, she was admitted to the Misericordia Hospital, because of edema of eight days' duration, elevated blood pressure, vertigo and headache. The onset of symptoms was sudden and spectacular. Studies on admission revealed hemoglobin 15 per cent; red blood cells, 1,100,000; white blood cells, 8,700; polymorphonuclears, 85 per cent, and lymphocytes, 15 per cent. Urea nitrogen 18 mg.; nonprotein nitrogen, 29 mg.; chlorides, 487 mg. On Nov. 3, 1933, the urea nitrogen was 32 mg.; creatinine, 1.1 mg. A transfusion of 100 c.c. of blood was given on Nov. 5, 1933, and 500 c.c. of blood was given on Nov. 7, 1933. On November 6, urea nitrogen was 26 mg.; blood sugar 85 mg. Urea clearance test, Nov. 7, 1933: first specimen, 79 per cent; second specimen, 59 per cent.

Reticulocyte Count: Nov. 8, 1933, 10 per cent.

Gastric Analysis: November 9, 1933.

	F.	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Free HCl	0	0	0	0	6	18	24	18	16
Total acidity	10	10	12	8	16	36	38	36	34

Reticulocyte Count: November 14, 1933, 19 per cent.

Blood count on Nov. 24, 1933, was: Red blood cells, 3,000,000; white blood cells, 11,300; hemoglobin, 46 per cent; polymorphonuclears, 78 per cent; lymphocytes, 20 per cent; monocytes, 2 per cent. Platelet count on Nov. 26, 1933, was 420,000.

Patient was discharged on Nov. 26, 1933. She was readmitted on Jan. 7, 1934, and delivered of a normal living female infant and was discharged on Jan. 17, 1934. During this confinement, specific gravity of urines ranged from 1.010 to 1.014. On Jan. 8, 1934, hemoglobin was 57 per cent; red blood cells, 3,000,000; white blood cells, 12,300; polymorphonuclears, 66 per cent; lymphocytes, 8 per cent; monocytes, 2 per cent; rod nuclears, 24 per cent, anisocytosis, poikilocytosis. On January 17, color index was 1.06. On March 16, 1934, patient was examined in postnatal clinic, when she complained of generalized weakness. Blood pressure was 110/70. She was referred to medical clinic, but made no response to follow-up cards.

On Sept. 20, 1934, she was admitted to Philadelphia General Hospital, service of Dr. P. Williams, because of a miscarriage. Her previous menses started June 17, 1934, and was of three days' duration. She claimed that on September 19, after lifting a heavy object, she experienced abdominal pain and passed several clots, followed by continuous bleeding. She had palpitation since her previous confinement,

and complained of recent hematemesis and a persistent cough since June, 1934. The preceding two months, she had had occasional nocturia with increased frequency. On admission, she seemed well nourished, but pale, with no dyspnea, jaundice or edema. Her cough was moist and nonproductive and there was slight cyanosis of lips. An occasional râle was heard on inspiration over left base. A systolic murmur could be heard at both the aortic and mitral areas, but no cardiac enlargement was elicited. The admission diagnosis was incomplete abortion with sinusitis and bronchiectasis. Blood count on Sept. 22, 1934: red blood cells, 1,705,000; hemoglobin, 35 per cent; white blood cells, 13,800; polymorphonuclears, 66 per cent; lymphocytes, 28 per cent; monocytes, 6 per cent. On Sept. 23, 1934, she was given 300 c.c. of citrated blood. The placenta was passed the same morning. Blood count on Sept. 25, 1934: hemoglobin, 40 per cent; red blood cells, 1,490,000; white blood cells, 32,000; polymorphonuclears, 67 per cent; lymphocytes, 30 per cent; monocytes, 2 per cent; eosinophiles, 1 per cent. No achromia, marked anisocytosis and polychromatophilia. Nucleated reds and high color index. It was thought that she had either a pernicious-like anemia of pregnancy or pernicious anemia. On September 26, she was given 300 c.c. of citrated blood and on September 27, 100 c.c. of citrated blood. She was discharged on Sept. 29, 1934.

On Feb. 7, 1936, the patient, six-months pregnant, was readmitted to the Prenatal Clinic of the Philadelphia General Hospital. She complained of frequent colds and persistent vomiting since the onset of pregnancy, and sudden dyspnea, palpitation and increasing weakness of one week's duration. Her diet excluded fruit juices and meat. Milk and vegetables were regurgitated. Because of the symptoms and marked pallor, macrocytic anemia of pregnancy was suspected and admission to the hospital was advised. On Feb. 14, 1936, she was admitted to the obstetric service of Dr. John A. McGlinn. Examination revealed a pallid, fairly well nourished, white female, aged 23 years, who did not appear acutely ill. No cyanosis was discerned. Sclerae were bluish and palpebral conjunctivae and buccal mucous membranes were quite pale. Venous pulsations in the neck were evident and systolic "bruit" was audible over the great vessels of the neck. The lungs were essentially negative to auscultation and percussion. Slight cardiac enlargement was present and a high pitched systolic murmur could be heard over the pulmonic and aortic areas. A loud, rough, systolic murmur and a soft diastolic murmur were heard over the mitral area. Blood pressure was 120/45. Pretibial edema was noted. The liver and spleen were not palpated. The uterus was definitely enlarged and reached the transumbilical level. She had vomiting and diarrhea on admission. Icterus index was 7. Red blood count on Feb. 16, 1936, was 740,000. Although 550 c.c. of citrated blood, diluted with 100 c.c. of saline, was slowly administered intravenously over a period of one hour and twenty minutes, she experienced immediate reaction with chills, dyspnea and cyanosis, with subsequent rise in temperature to 105.5° F. She responded to symptomatic treatment, but her condition was rather precarious. The next day, February 17, the diarrhea and vomiting had ceased, gallop rhythm was elicited and the left cardiac border extended to the anterior axillary line. Blood pressure was 115/40. A transfusion at 10 P.M. on Feb. 17, 1936, was followed, an hour later, by a reaction characterized by a sense of sternal constriction and a dry distressing cough with wheezing. This reaction was partially relieved by symptomatic treatment.

A transfusion at 8 P.M. on Feb. 19, 1936, was stopped because of an immediate reaction similar to that of Feb. 17, but accompanied by vomiting. The liver and spleen were palpable. Retinal hemorrhages were found scattered throughout both fundi. Improvement was slow but steady. The gastric analysis revealed:

	FASTING	10 MIN.	20 MIN.	30 MIN.	40 MIN.	50 MIN.	60 MIN.
Free HCl	0	15	17	21	0	0	0
Total HCl	20	26	31	40	24	22	20

On March 5, 1936, her clinical improvement appeared so satisfactory that she was discharged the next day. In subsequent clinic check-up, her weight increased from 123½ pounds on March 13 to 138¾ pounds on May 1. Ankle edema persisted and vomiting was a conspicuous symptom. She was re-admitted to the Obstetrical Divi-

TABLE I. MRS. K.

DATE, 1936	HEMOGLOBIN %	MILS R.B.C. C.MM.	W.B.C. C.MM.	MYELOCYTES	JUVENILES	STABS	SEGMENTERS	TOTAL NEUTROPHILES	LYMPHOBLASTS	LARGE LYMPHOCYTES	INTERMEDIATE LYMPHOCYTES	SMALL LYMPHOCYTES	TOTAL LYMPHOCYTES	MONOCYTES	EOSINOPHILES	BASOPHILES	LIVER EXTRACT C.C.	TRANSFUSION, BLOOD C.C.	ERYTHROBLASTS	POLYCHROMATOPHILIA	MACROCYTES	RETICULOCYTES	PLATELETS, THOUSANDS	VOLUME INDEX
2/16	20	0.74	14,000	0	0	22	58	80	0	6	0	14	20	0	0	0	2	550	+	+	+			1.85
2/17	20	0.84	24,700	0	0	64	26	90	0	2	0	6	8	2	0	0	2	450	0	+	+			
2/17	20	0.89	19,200	0	0	20	60	80	2	0	0	18	20	0	0	0			0	+	+			
2/18	25	1.01	11,350	0	0	8	68	76	0	0	0	20	20	2	0	0	2		0	+	+			
2/19	30	1.30	16,200	0	0	42	44	86	0	2	0	8	10	4	0	0		350	0	+	+	1.0		
2/20	30	1.13	12,850	0	0	40	40	80	0	0	0	20	20	0	0	0	4		0	+	+		60	1.27
2/21	30	1.16	16,700	0	0	10	30	40	0	0	0	40	40	20	0	0	4		0	+	+	1.0		1.28
2/24	30	1.19	10,300	0	0	20	32	52	0	2	0	42	44	4	0	0	4		0	+	+	8.0		
2/25	30	1.39	11,800	0	3	9	30	42	0	6	0	34	40	18	0	0	4		+	+	+	5.0		
2/26	40	1.99	9,300	0	0	32	32	64	0	6	0	26	32	4	0	0	5		0	+	+	3.6		
2/28	40	1.98	12,400	0	0	36	30	66	0	2	0	28	30	4	0	0	5		0	+	+			
3/ 2	51	2.22	14,300	0	0	26	34	60	0	8	0	20	28	12	0	0	3		0	+	+	3.0		
3/ 5	53	2.53	19,300	0	0	42	42	84	0	0	0	10	10	6	0	0	3		0	+	+	1.2	200	
3/13	55	2.55	8,300	0	0	26	40	66	0	6	0	24	30	2	2	0	3		0	+	+	2.2		
3/26	45	2.24	10,900	0	0	50	36	86	0	0	0	4	4	2	4	0	3		0	+	+	2.0		
4/ 8	52	2.47	8,800	0	0	36	44	80	0	2	0	10	12	6	0	0	3		0	+	+	1.0		
5/ 4	25	1.10	8,800	0	0	32	52	84	0	0	0	14	14	8	0	0	1		0	+	+	1.0		
5/ 7	25	1.00	9,000	0	0	26	38	64	0	4	0	24	28	2	4	0	3		0	+	+	2.0	50	
5/ 8	25	1.03	19,000	0	2	34	28	64	0	2	0	28	30	4	4	0	3		0	+	+	2.5	50	
5/12	25	1.16	24,800	0	0	28	32	60	0	6	0	32	38	2	2	0	6		0	+	+	5.0		
5/14	35	1.84	16,000	0	0	46	40	86	0	0	0	10	10	4	0	0	10	500	0	+	+	4.5		
5/16	35	1.87	27,500	0	2	42	36	80	0	6	0	10	16	4	0	0	10	550	0	+	+	2.6		
5/18	40	2.15	22,000	0	0	30	38	68	0	8	2	22	32	0	0	0	10		0	+	+	2.0	100	
5/28	75	3.15	10,700	0	0	28	38	66	0	2	0	28	30	4	0	0	6		0	+	+	1.0		
9/23	75	3.17	13,800	0	0	36	32	68	0	4	2	14	20	4	4	4	6		0	+	+	1.0	250	

TABLE II. BABY JOAN K.

DATE, 1936	HEMOGLOBIN %	MILS R.B.C. C.MM.	W.B.C. C.MM.	MYELOCYTES	JUVENILES	STABS	SEGMENTERS	TOTAL NEUTROPHILES	LYMPHOBLASTS	LARGE LYMPHOCYTES	INTERMEDIATE LYMPHOCYTES	SMALL LYMPHOCYTES	TOTAL LYMPHOCYTES	MONOCYTES	EOSINOPHILES	BASOPHILES	LIVER EXTRACT C.C.	TRANSFUSION. BLOOD C.C.	ERYTHROBLASTS	POLYCHROMATOPHILIA	MACROCYTES	RETICULOCYTES	PLATELETS, THOUSANDS
5/30	25	1.41	14,600	6	6	34	14	60	0	2	0	24	26	11	2	1	0.0		+ +	+	+	1.0	320
6/ 1	20	0.96	12,200	4	6	40	22	72	0	4	0	16	20	6	2	0	0.0					1.0	300
6/ 3	25	1.25	16,900	12	14	36	20	82	0	8	0	10	18	0	0	0	2.0	65	+ +	+	+	1.0	340
6/ 4	25	1.10	14,200	8	10	32	30	80	0	6	2	8	16	4	0	0	2.0	120	+ +	+	+	1.0	300
6/ 5	78	3.98	11,200	0	0	44	28	72	0	6	0	14	20	4	4	0	2.0		+ +	+	+	1.0	340
6/10	50	2.20	9,800	0	16	34	16	66	0	4	2	6	12	18	4	0	2.0		+ +	+	+	2.0	320
6/13	35	1.82	10,200	2	8	38	15	63	0	2	2	8	12	22	3	0	2.0	60	+ +	+	+	2.0	302
6/16	25	1.36	15,200	2	2	22	14	40	0	10	0	22	32	28	0	0	2.0		+ +	+	+	3.0	100
6/18	30	1.60	12,900	2	4	16	15	37	6	45	5	2	58	3	2	0	2.0	60	+ +	+	+	2.5	60
6/21	25	1.26	10,000	0	0	7	2	9	5	83	1	0	89	1	0	1	0.5		+ +	+	+	5.0	80
6/26	35	1.80	10,100	0	0	10	4	14	4	70	2	4	80	4	2	0	0.5	60	0	+	+	3.0	100
6/29	40	2.10	10,000	0	4	8	6	18	0	26	0	42	68	12	0	2	0.5		0	+	+	2.5	120
7/11	45	2.41	9,800	0	0	20	10	30	4	10	6	40	60	6	4	0	0.5	60	0	+	+	1.5	150
7/13	52	2.52	8,000	0	0	26	12	38	2	6	0	44	52	6	0	4	0.5		0	+	+	1.0	160
7/15	50	2.48	9,200	0	0	30	14	44	4	10	6	30	50	4	2	0	0.5	50	0	0	+	1.0	180
7/16	52	2.58	7,300	0	0	40	16	56	0	10	4	20	34	10	0	0	0.5		0	0	+	2.5	220
7/18	50	2.60	8,400	0	0	24	10	34	6	10	10	30	56	6	4	0	0.5	20	0	0	+	2.0	224
7/22	70	3.16	9,900	0	0	18	4	22	2	18	0	46	66	8	4	0	0.5		0	0	+	1.0	250
7/23	70	3.20	8,900	0	0	20	10	30	2	14	16	30	62	6	2	0	0.5	40	0	0	+	1.0	230
7/30	75	3.35	8,800	0	0	23	19	42	0	4	10	36	50	5	3	0	0.5		0	0	+	1.0	240
9/23	78	3.77	8,000	0	0	20	42	62	0	4	6	16	26	12	0	0	0.0		0	0	+	1.0	250

sion May 2, with a history of a severe cough of three weeks' duration. Examination revealed her chest to be full of rhonchi, ankles were severely edematous and mucous membranes and nailbeds were very pale. Liver and spleen were not palpable and fetal heart sounds could not be heard. Her red blood count was slightly above 1,000,000 per c.mm. Liver extract was started but transfusion was deemed necessary. Transfusions on May 12 and 14 were followed by severe reactions. Following a spontaneous rupture of the membranes and preceded by a few pains, a precipitous delivery occurred in bed on May 15, 1936. Following delivery the patient improved rapidly and was discharged June 3, 1936. In September, 1936, her blood showed 3,000,000 red blood cells per c.mm. and gastric analysis revealed:

	FASTING	15 MIN.	30 MIN.	45 MIN.	60 MIN.	75 MIN.	90 MIN.	105 MIN.
Free HCl	0	10	14	22	38	42	41	empty
Total HCl	5	16	25	39	61	63	61	empty

Baby Joan K.: was born May 15, 1936, weighing four pounds, fifteen and one-half ounces and was apparently in good condition. The infant received breast milk and a complementary formula. The infant's progress was good except for increasing waxy pallor. The liver was 4 cm. below the costal margin and the spleen 1 cm. below the costal margin. The blood count, on June 1, revealed a severe anemia. Therapy consisted of liver extract, antirachitics, orange juice, and ferrous iron therapy. The infant regurgitated moderately, especially orange juice and iron. Following transfusions her complexion would improve and listlessness would disappear, although mild temperature reactions occurred. Hemograms demonstrate the blood pictures of the mother and infant and their response to treatment.

DISCUSSION

Macrocytic anemia encountered during pregnancy has been divided into three types,[6] tropical nutritional anemia, true Addisonian anemia complicated by pregnancy, and macrocytic anemia induced by pregnancy. It is the latter type of anemia which concerns us here. It is a rare complication of the gravid state. Only one case has been encountered on the Maternity service of the Philadelphia General Hospital. Hematologically, macrocytic anemia of pregnancy is indistinguishable at times from "true" pernicious anemia. It is now generally believed, that this condition is due to a dietary deficiency and the old theory that this condition is due to some product of gestation is no longer tenable. Elsom and Sample[7] have produced macrocytic anemia by means of diets deficient in vitamin B complex, and prompt relief has been obtained by the administration of vitamin B complex and liver, with subsequent delivery of normal full-term infants. The response of our patient to liver therapy may be considered inadequate and her severe reactions to transfusions precluded their further use. The reticulocyte response was poor both during pregnancy and after parturition. The reticulocyte response as an index of effectual therapy is well recognized. Minot and Castle[8] state, "In the analysis of the physiologic basis of various types of nutritional deficiency anemias, daily observation of the course taken by the reticulocytes probably constitutes the best single criterion. Thus, in definitely anemic patients the failure of a reticulocyte response to appear after parenteral injection of liver extract or after oral administration of iron or orange juice may be taken to indicate that there is not a deficiency of these substances." We can, therefore, assume either that a specific need for the liver was not indicated or that an inadequate dose or an impotent

extract was used. Nevertheless, the mother did improve after delivery, when there was a cessation of vomiting and diarrhea and better utilization of a balanced diet.

The deficiency factor which produced the anemia in the mother may possibly have been likewise deficient in the infant. It appeared that the maturation of the erythron was arrested at a fetal level, because of the infant's inability to utilize a factor which it could not obtain in utero. In fact, there appears to have been little response to combined therapy and the transfusions seemed only to carry the infant over until such a time as its own erythropoietic system could function at a more mature level. The infant's reticulocyte response was definitely poor in spite of marked anemia. Once a higher level of maturation of the infant's red blood cells was attained, probably conditioned by dietary intake of the deficient factor, steady improvement was noted. Oddly enough there was not an "adequate" reticulocyte response in the recovery phase. We can only say that the erythropoietic system was either depressed or inhibited in some inexplainable manner and improvement occurred only when this was overcome. Why such factors should work selectively on the erythropoietic system does not seem explainable, except by some mechanism such as produces pernicious anemia in adults. The anemia of the infant may be difficult to classify. We believe that we may be justified in calling this a "hypoplastic" anemia, but feel as many others have before us, that it is more important to arrive at an understanding of the process than to give it a name.

SUMMARY

The relationship of macrocytic anemia of pregnancy with a severe anemia of the newborn is herein reported, with a discussion of the etiologic factors involved. We believe that the anemia of both the mother and the infant is due to a dietary deficiency.

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THE TREATMENT OF EARLY ABORTION*

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THE term abortion is used to represent the loss of a pregnancy before twenty-eight weeks of gestation have passed. The term, however, is confusing because our present archaic laws require us to register as births all pregnancies terminating after twenty weeks of gestation. We are, therefore, using the term early abortion as meaning the expulsion of the products of conception before thirteen weeks, and we will confine our discussion to such cases. If the term late abortion is used, we mean the loss of a pregnancy between thirteen and twenty-eight weeks.

It has been stated by Taussig[1] that abortion is the greatest single factor in fetal and maternal mortality and also that one out of every four or five pregnancies terminates in fetal death through abortion and that two out of every five maternal deaths can be ascribed to an abortion. Macomber reports one abortion to every 3.4 confinements. Kapp 1 to 2.5 and Plass polling 81 country physicians says about 1 out of every 5 for the rural sections.

We have no way of obtaining the correct figure for this series but while these 1,114 early abortions were being handled, resulting in 985 completed cases, there were 258 late abortions and 12,294 deliveries in the Evanston Hospital. This gives a ratio of about 1 abortion to 9.8 deliveries. In the private practice of one of us (C. E. G.), early (4.9 per cent) and late (3 per cent) abortions combined were 7.9 per cent of all cases coming for care during the past nine years, in other words, 1 abortion to 11.6 deliveries.

The higher figures mentioned above may be representative of the country as a whole but cannot be taken as an example of what is true of all groups of people, as we shall show from a study of early abortions at the Evanston Hospital during the past fifteen years.

Among a fairly intelligent group of women who desire babies and who exercise good care in order to get them, the figures are much lower. The principal factor in abortion deaths is criminal interference and next comes improper conduct of abortion by the physician. If we eliminate the crime factor and if we accept the statement that fully 60 per cent of all early abortions are due to faulty development of the germ plasm, abortion at once becomes a minor problem.

A large factor in the incidence of abortion today is the lack of knowledge of such matters on the part of the laity. Our women know very little concerning the physiology of pregnancy. They attend schools with as high a scholastic ranking as those attended by the men, but the subjects taught and emphasized are not those pertaining to reproduction and

*Presented at a meeting of the Chicago Gynecological Society, January 20, 1939.

the home. The men, on the other hand, come to positions in life well equipped with a vast store of information and much better prepared to face the problems they meet. If we could teach our women the care which is sometimes necessary to retain an early pregnancy, rather than be called upon at the last minute to find the patient aborting and referring to the accompanying flow as "menstruation," we would probably have fewer abortions. The average young woman has a fair knowledge of contraception, but she knows little or nothing of the ravages of abortion and gonorrhea and only because she has received no such teaching.

This paper deals with the management of early abortion and not its cause, hence no further comment will be made on prevention. Suffice it to say that we probably have only 40 per cent of the cases of threatened abortion that could or should be prevented—the embryos in the other 60 per cent have not developed properly and should be expelled.[2]

A factor in prevention still holding number one position is bed rest and whenever one is called to attend a patient having symptoms of abortion, he should insist upon bed rest and the patient should be kept in bed until several days have elapsed with no further signs of bleeding or cramps.

Since Lackner[3] and others have shown that morphine and its derivatives may cause uterine contractions, the authors have used pentobarbital as a sedative, with good results. Morphine and codeine many times may also cause nausea and vomiting; the barbiturates do not.

A great deal has been written about the use of progesterone or the luteinizing hormone and its ability to quiet uterine contractions, thus preventing abortion. From a clinical standpoint it seems to do some good; however, it is very difficult to prove its effectiveness clinically, and it is also quite expensive. In our experience, there have been times when we felt certain that it had a quieting effect upon uterine contractions even in women with a history of repeated abortions and whose personal reactions and experiences were worth considering. On the other hand, one of us has seen two cases where its administration led to a prompt increase in pain and bleeding, followed by rapid abortion. Our knowledge of the endocrines and our ability to prepare them are still in the embryonic stage of development.

Because these products are so expensive, we have during the past year been giving them hypodermically at the beginning of the treatment only—the treatment is then changed to corpus luteum by mouth. However, when a patient first bleeds, and more especially if she has cramps, she is given three and four units of proluton every twenty-four hours regardless of the cost. This is accompanied by fairly large doses of pentobarbital, 3 to 4.5 gr. at night and 1.5 gr. about noon. As time goes on, the amount of proluton is decreased and after several days the patient is given 5 gr. of lutein by mouth three times a day and the sedative is stopped. We prefer that the patient go to the hospital if at all possible; if not, she is asked to have a nurse with her at home. If neither is possible, the injections are given by a visiting nurse or the attending doctor.

We have had little experience with wheat germ oil. It has been used, but always in conjunction with proluton, calcium, and sedatives, and we

are not in a position to evaluate this product. After reading the literature on its use in the prevention of abortion, we concluded that there has been no satisfactory clinical work done with it when it is used alone in treating a series of such cases.

We still believe that the greatest single factor in prevention is bed rest with sedation. This report covers a period of fifteen years and during the greater part of this period neither hormone treatment nor wheat germ oil had been in use. From Table I, it is found that 135 patients entered the hospital with a diagnosis of threatened abortion and 124 of these left the hospital still pregnant. The 11 who aborted did so in the first five-year period.

One often hears figures on the incidence of abortion quoted and in Table VI, the record is shown of private patients treated by one of us during the past nine years. Our patients come early for care—about eight or nine weeks pregnant at their first visit. If only approximately 5 per cent have early abortions and three-fifths of these are to be regarded as developmental defects, then this group of women had a loss amounting to 2 per cent that might have been saved during early pregnancy.

It is essential in the proper care of such cases to make a fairly accurate estimate of the amount of blood lost. Fatalities have occurred because no one was aware of the importance of this knowledge, and often the physician has been compelled to interfere when a false statement was being made by the patient or her attendants. Regardless of how slight the bleeding, the patient should be instructed to use a vessel and to save all pads so that the physician can see them and make his own deductions with reference to the amount of blood loss.

Now we come to the question of how much blood loss should be tolerated before terminating the pregnancy. The size of the uterus, the age of the patient, the parity, the general state of health and the patient's reaction, all must be taken into consideration. Personally, we feel that all things considered, early interference will give the best results. This seems to be the opinion of most observers whose work is being reported in this paper. The 1,114 patients upon which this paper is based were treated by 49 doctors, although 73 per cent of these patients were attended by 6 men. The maternal mortality for the entire group, including 65 classed as criminal, is only 0.35 per cent, and if we deduct the 129 patients who left the hospital still pregnant, the mortality is 0.40 per cent. The maternal mortality for 751 operative cases, exclusive of criminal abortion, is only 0.26 per cent. This compares favorably with our maternal mortality for delivery which was 0.17 per cent for the past ten-year period.

Before considering evacuation of the uterus, one must always attempt to ascertain the presence of infection, for the majority of all fatalities are due to sepsis. Hillis and others have made the rule that the temperature should be normal for five days before curettage, if this may be possible. It is only the rare case that is infected and at the same time bleed-

ing enough to endanger the patient's life. However, there are many patients who should not be operated upon even after five days of normal temperature when laboratory evidence may indicate there is no infection.

Most women desiring children and willing to cooperate in their treatment are not infected, as is shown in Tables I and II; however, we did show reasonable conservatism by waiting, in 204 patients, an average of from three to four weeks before they were admitted to the hospital. These figures are shown in Table III. The ability to detect a hidden infection or a potentially infected case requires not only thorough laboratory work but considerable clinical experience as well.

The routine followed at the Evanston Hospital is as follows:

If possible we wait until the cervix is somewhat dilated. Morphine ⅙ gr. and atropine 1/150th gr. is given by hypodermic before the patient goes to the operating room; then she is given a general anesthetic using ethylene. We find that the average patient does not like to be conscious throughout any operative procedure if sleep is possible and safe, and so we have available at the Hospital four trained anesthetists. The patient is then draped, and after this the contents of the uterus are removed with placental forceps. The uterus is then injected with pituitrin by means of a long needle passed through the cervix. A large sharp curette is then used to remove any fragments of placental tissue and the uterus and vagina are packed with gauze. If we have interfered because of bleeding and we suspect contamination, the curettage and packing are dispensed with.

TABLE I. OPERATIVE INCIDENCE OF EARLY ABORTION

ENTRANCE DIAGNOSIS	NUMBER	OPERATED			NOT OPERATED		
					SPONTANEOUS		REST PALLIATIVE
Incomplete	643	605	C	(93.7%)	26	(4.0%)	9
		2 hysterectomies					
		1 laparotomy					
Threatened	135	4	C	(3.0%)	7	(5.2%)	124 still pregnant
Inevitable	73	51	C	(70.0%)	19	(26.0%)	3 still pregnant
Complete	108		—		108	(100.0%)	—
Therapeutic	74	64	C	(85.5%)		—	—
		10 hysterotomies					
Criminal	65	21	C	(32.0+%)	14	(21.0%)	—
Missed	16	14	C	(87.5%)		—	2
Total	1,114	759	C	(69.0%)	174	(15.6%)	14

TABLE II. MORBIDITY AND MORTALITY OF EARLY ABORTION

ENTRANCE DIAGNOSIS	NUMBER	DEATHS	FEBRILE CASES 101 UP 1 DAY OR MORE		AV. NUMBER DAYS FEBRILE
Incomplete	643	1	72	(11.0+%)	1.6
Threatened	135	–	6	(4.4%)	2.6
Inevitable	73	–	5	(6.8%)	1928-1938 1
Complete	108	–	11	(10.0+%)	4.8
Therapeutic	74	1	15	(2.2%)	1.4
Criminal	65	2	22	(33.8%)	5.2
Missed	16	–	1	(6.2%)	–
Total	1,114	4 (0.35%) *(0.40%)	132	(11.2%)	–

*Deducting 129 who went home pregnant.

TABLE III. DURATION OF SYMPTOMS BEFORE ENTERING THE HOSPITAL

DIAGNOSIS	NUMBER	DURATION OF SYMPTOMS AVERAGE NO. OF DAYS	
		2 WEEKS AND OVER	UNDER 2 WEEKS
Incomplete	643	160 av. 24.2 days	413 av. 3.3 days
Threatened	135	92 av. 25.4 days	65 av. 2.4 days
Inevitable	73	12 av. 23.1 days	50 av. 3.1 days
Complete	108	14 av. 36.2 days	72 av. 3.0 days
Therapeutic	74	6 av. 58.0 days	1 av. 7.0 days
		(1928-1938)	
Criminal	65	17 av. 26.8 days	32 av. 4.6 days
Missed	16	3 av. 28.0 days	5 av. 3.6 days
		(1928-1938)	
Total	1,114		

The reasons presented for therapeutic abortion are given in Table IV, and we presume some criticism will be forthcoming as thyroid disease, heart disease and diabetes are all questionable indications. It is difficult, even for one examining the charts, to tell fully the extent of the disease; however, the rule that at least two men must state in writing that the procedure is absolutely necessary, has always been followed.

The most difficult cases to manage and those showing the highest mortality are the cases of criminal abortion, either complete or incomplete. Only about 6 per cent of our cases were classified as such but these fur-

TABLE IV. REASONS FOR THERAPEUTIC ABORTIONS

There were 74 therapeutic abortions during this fifteen-year period. Sixty-four were curetted and ten had hysterotomy done.

Causes for therapeutics were as follows:

Toxemia	11	Tuberculosis	8
Thyroid	6	Pernicious vomiting	9
Psychoneurosis	2	Pernicious anemia	1
Heart	18	Carcinoma of bowel	1
Kidney	12	Osteomyelitis	1
Diabetes	1		
Strangulated ovarian cyst and recent laparotomy			1
History of malformations			3

TABLE V. CRIMINAL ABORTIONS*

	FIRST 5 YR.	SECOND 5 YR.	THIRD 5 YR.
Operated	7	12	2
Spontaneous	9	2	3
Not reported	5	17	8
Total 65	21	31	13

*Note: Deaths (2), both unoperated.

TABLE VI. INCIDENCE OF ABORTION—PRIVATE PATIENTS

During the nine-year period just ended, 4.91 per cent aborted before 13 weeks, of these:

37 per cent were complete spontaneous

63 per cent were incomplete and required dilatation and curettage

Three per cent terminated between thirteenth and twenty-eighth weeks, of these:

69.7 per cent were spontaneous

30.3 per cent were incomplete and required operative interference

nished 50 per cent of the mortality. It is a fairly safe procedure to always refrain from any surgical interference in such cases unless driven to it by hemorrhage or some other emergency. However, as can be seen in Table V, at least 21 of the 65 patients were operated upon. The two patients in this group who died were not operated upon.

Brief case reports of the four deaths in the series of 1,114 cases follow:

CASE 1.—Patient, aged 31, para iv, was about seven weeks pregnant. She entered the hospital in shock, March 5, 1929. Pulse 110. Temperature 98.6° F. At times her pulse was not obtainable. Symptoms: bleeding four days, Hg 57 per cent, red count 3,290,000, she was admitted at 10 A.M. Dilatation and curettage and the uterus was packed at 10:15 A.M.; 2,000 c.c. of dextrose in Ringer's solution 5 per cent during afternoon. At 5 P.M. her temperature was 104° F.; pulse, 132; respiration, 26. She died at 9:45 P.M. Microscopic diagnosis: Infected and necrotic placental tissue. Caffeine by hypodermic 6 times. No morphine. Not transfused. No autopsy.

CASE 2.—Patient was admitted Jan. 19, 1930 and died January 20. Patient said a midwife inserted a rubber catheter two days before she entered the hospital and the following day the midwife did a curettage and packing. Generalized peritonitis when first seen. Temperature 104° to 106° F. White blood count 21,000. Pulse 120 to 156. Autopsy: Ectopic pregnancy. Fibrinopurulent hemorrhagic general peritonitis and metritis. Blood culture: Hemolytic streptococci. (The midwife was convicted and sentenced.)

CASE 3.—Patient entered the hospital on the evening of Aug. 20, 1930 and died on the morning of August 22. She was three months pregnant. She had been vomiting for six weeks. She was at home and not attended by any physician. Urine 40 per cent albumin, casts, red cells and sugar +. Temperature 98.6° F. Pulse 90 on entrance. 3000 c.c. of dextrose in Ringer's by vein and 1000 c.c. normal salt solution by proctoclysis first twenty-four hours. She passed only 25 c.c. of urine. Pulse went up to 120 and patient passed into shock. Diagnosed acute nephrosis. Uterus was emptied as quickly as possible. Patient remained in shock and died five hours later. Considerable blood was lost but a transfusion was not given.

CASE 4.—Patient, aged 27, para i, two months pregnant, entered the hospital July 26, 1935 and died August 6. She inserted a slippery elm herself and fever began twenty-four hours later. She was admitted to the hospital three days later, and developed general peritonitis. Usual peritonitis treatment was given with no surgical procedures, except numerous venoclyses and two blood transfusions. No autopsy was performed but the coroner stated that the uterus contained multiple abscesses and infected necrotic placental tissue.

COMMENT

During the past fifteen years, 1,114 cases of early abortion were cared for at the Evanston Hospital. Four patients died, a mortality rate of 0.35 per cent for the entire series or 0.40 per cent if 1,129 patients who were discharged still pregnant are eliminated. Sixty-nine per cent of the entire series were operated upon. Deducting the therapeutic abortions and those still pregnant when discharged this percentage changes to 86.3. The total morbidity was 11.3 per cent. During the same period there were 6 hydatidiform moles and 95 ectopic pregnancies and 258 late abortions.

CONCLUSIONS

1. Among a fairly intelligent class of women where a large majority want babies, early abortion occurs in about 5 per cent and late abortion in about 3 per cent.

2. If one accepts the fact that fully 60 per cent of all early abortions are due to faulty germ plasm, we must conclude that only 2 per cent of our women will lose their pregnancy during the first three months, which might otherwise have been preventable.

3. The risk of early abortion should be below one-half of 1 per cent.

4. A high operative incidence in such cases does not appear to increase morbidity or mortality.

5. The mortality for early abortion, exclusive of criminal abortion, should be no higher than that for delivery.

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DISCUSSION

DR. DAVID S. HILLIS.—I desire to report on part of the year's work at Cook County Hospital on abortions, approximately a six months' experience. Patients at this hospital are very different from those considered in Dr. Galloway's report. Accurate information regarding the relative number of spontaneous and criminal abortions is practically impossible to obtain, but we do know that a large proportion of the cases in Cook County Hospital are criminal abortions. The policy in this hospital is to treat all cases on this basis; any mistakes made are on the side of safety. It is well known that the second invasion of the aborting uterus is dangerous until the patient has been temperature-free for five days and during this year we have found one exception to this rule. Approximately four out of five of all patients admitted are fever-free and are classed as nonseptic cases. About 75 per cent of these are allowed to empty the uterus themselves with the aid of quinine and pituitrin in small doses. If the bleeding is prolonged or excessive and involution does not progress normally, the uterus is evacuated with a dull curette or ovum forceps after the temperature has been normal for five days. Septic abortions are not emptied except when hemorrhage endangers life. When bleeding is severe the os is practically always found to be well dilated, permitting removal of the contents by means of ovum forceps and with a minimum of trauma. If severe bleeding does not occur, supportive treatment, intravenous fluids, blood transfusions, and sedatives are used. Sulfanilamide is now being given to alternate cases in the ward.

Routine packing of the uterus is not done on this service. The uterus is packed only in rare cases in which bleeding is so profuse during a curettement that it must be stopped immediately. Packing the uterus interferes with contraction, retraction, and drainage, and if the uterus is empty it will not bleed. During the past twenty-five years in this ward no uterus has been packed except for hemorrhage.

The deaths on this service belong to two groups:

1. Those who are admitted in a terminal state with peritonitis or septicemia. The deaths in 1938 included seven such patients who died within twenty-four hours.

2. The second group that contributes to mortality are those that are curetted in the ward on account of excessive hemorrhage. One patient died following curettage after the temperature had been normal for five days. A gangrenous placental polyp was found at post mortem. This case in our experience is one of the rare exceptions to the rule that it is safe to curette a patient after five days of normal temperature.

DR. WILLIAM H. BROWNE.—At the Research Hospital we have an entirely different problem from that in private practice, in a private hospital or in a large charity hospital such as the Cook County. Because of the dearth of beds for obstetrics those patients who might come in as emergencies are not admitted but are usually shifted to the Cook County Hospital unless they have been previously regis-

tered in the dispensary. Consequently, the incidence of abortions at the Research Hospital is astoundingly low. Furthermore, these patients apparently wish to keep their pregnancies because they have come to the dispensary and registered and subsequently developed hemorrhages. We do not have many criminal abortions. In the last six years 54 patients were admitted to the hospital for the management of abortions. This does not constitute as early a group as Dr. Galloway reported and is an incidence of slightly less than 1 per cent. This low figure is explained by the fact the patients register first.

We feel in the management of these cases where the onset is presumably spontaneous that the point of departure is the life or death of the fetus. Consequently, if we can determine that the fetus is alive and if no abortion is in progress as evidenced by rectal examination, all our efforts are conservative in the attempt to save the pregnancy. If, after twenty-four hours, we find that the fetus is probably dead and retained, all efforts are aimed at aiding the uterus in evacuating its contents. This diagnosis of the life and death of the pregnancy is arrived at from the history, symptomatology, and by the use of the Friedman test for pregnancy. If the test comes back positive we know that we have presumably living, growing placental tissue. We are not sure that the fetus is still alive, but we feel that in a fair percentage of cases it is. If we get a negative reaction we feel that the diagnosis of suspected abortion is questionable. Those cases are treated actively to check the bleeding. There is an intermediate group that gives a faint reaction on the ovaries of the rabbit. Dr. Rezek has reported this reaction as a dead fetus reaction. If the ovary of the rabbit is placed on a slide and held up to the light you will see a faint circle of hyperemia around the follicle. That test is not infallible but at the Research Hospital it has enabled us to make a diagnosis of a dead fetus and to switch the management from conservative to radical, and enable the patient to make a prompt recovery.

A certain group of cases have been treated with progestin. The morphine that Dr. Galloway mentions is used sparingly on the basis that it may produce uterine contractions. We feel that the diagnosis of a dead fetus is essential in the management of abortion, so that we will not be giving progestin to hold a dead fetus in the uterus.

DR. FRED O. PRIEST.—We have reviewed the charts of early abortions at the Presbyterian Hospital during the past five years. These include the private patients, the hospital clinic obstetric patients and those from the Out-patient Department of Rush Medical College requiring hospitalization. Our number of incomplete abortions completed by medical management is small, since these patients, private or otherwise, are not hospitalized if bleeding is controlled by oxytocics given at home. The small number of threatened abortions is due to the fact that, first, all uncontrolled cases are transferred to the inevitable or incomplete classification and are listed in the above column; second, most of our threatened abortions are treated at home, even among private patients. This management consists of absolute bed rest, sedation, both morphine and barbiturates and more recently wheat germ oil. In private practice proluton is also given. Patients who have had repeated abortions are placed on a modification of this regime when pregnancy is diagnosed, even before symptoms of a disturbed pregnancy exist. We believe that conservative treatment should not be continued where symptoms are prolonged or where bleeding becomes heavier than at an ordinary menstrual period. We are, of course, influenced in this by the length of the sterility period and the patient's desire for the child.

DR. PAUL W. WOODRUFF.—At the Chicago Lying-in Hospital the same remarks can be made about the type of patients as Dr. Browne made. Our cases are mostly registered cases, thus our incidence of criminal abortion and the general incidence of abortion are low. I will limit the discussion to the treatment of incomplete and inevitable abortion.

The treatment of threatened abortion is similar to that given by Dr. Galloway except that we use morphine and atropine as sedative and antispasmodic drugs, while

progestin is used more in cases of habitual abortion. Bed rest, I feel, is the most important part of the treatment. Wheat germ oil and thyroid extract are also incorporated into the treatment of habitual abortion.

In a series of 397 cases the upper incidence of intentional abortion was 14 per cent; in another 6 per cent the abortion was attributed to toxemias, habitual abortion, or over-activity. There were 83 therapeutic abortions or 20 per cent included in this group of 397 cases.

Our treatment of inevitable and incomplete abortion consists of bed rest, which is the most important part of the treatment. If the symptoms are mild the patient is usually treated at home rather than being brought to the hospital, because we feel that possibly the trip to the hospital may be a strong factor in changing a threatened abortion into an inevitable abortion. On admission the patient is kept at bed rest for seventy-two hours, watching the temperature, pulse, and the white blood count. Abdominal examination is done to rule out any extension of infection to the parametria and peritoneum. The uterus is evacuated at the end of this period if the above criteria are normal. If abnormal, observation is continued until the patient is normal. If the bleeding is profuse the uterus must be emptied at once. General supportive treatment is given. An important aid is the use of blood transfusions, preoperatively as well as post-operatively. On admission to the hospital 21 per cent of the 397 patients had fever.

At operation careful examination is made to rule out any extension of infection, pelvic abscess, or adnexal pathology. The cervix is exposed and a uterine culture is taken. It is interesting that 40 per cent of positive uterine cultures were due to anaerobic streptococci and only 6 per cent to hemolytic streptococci. The evacuation of the uterus is done with a sponge or ovum forceps and a large dull curette. We usually give 1 c.c. of pituitrin into the uterus before curetting. The uterine cavity is swabbed out with an iodine soaked gauze sponge. We avoid any packing of the uterus and any extensive instrumentation. The uterus was emptied in 75 per cent of our series. If we exclude the therapeutic abortions the incidence of emptying the uterus is 69 per cent.

Postoperatively, general supportive treatment is given and again I emphasize blood transfusions. We routinely tranfuse a patient if the hemoglobin is below 10 gm. Of course, if the patient shows evidence of infection postoperatively, she is treated as a case of peritonitis. Otherwise, general supportive treatment is the routine.

The average number of postoperative days is four for nonseptic cases. Sulfanilamide is used in our clinic only in cases of proved etiology and where the organism is known to respond to sulfanilamide.

The morbidity was 13 per cent. Three patients died, two having been admitted with obvious severe infections, self-induced. In these two cases no operative treatment was carried out by us. The third patient who died had a therapeutic abortion. However, the death was due to hyperemesis gravidarum, the patient being comatose at the time of operation and dying eight hours later.

DR. HAROLD O. JONES.—I wish to present the other side of this problem. First, it seems to me that the results of the methods of treatment are questionable. We are convinced that if a certain number of these patients are left alone a great many pregnancies will be saved. Time will show whether it is a threatened abortion or an inevitable abortion. Consequently I think they are entitled to all the time they need to keep the products of gestation in the uterus.

Second, we believe that infection is associated with practically all these conditions. There is no way of determining the virulence and the degree of infection. Our plan of management is just the opposite from what was stated here tonight. Our patients are treated conservatively and left absolutely alone. If they come in bleeding profusely and there is tissue in the cervix, the tissue is removed but on no account do we curette.

The other thing that I think is important is this: from the paper of the essayists one would think this a very simple procedure. If one knew the number of cases of perforation of the uterus that occur following curettement, one would be very cau-

tious about doing a curettage. Another thing that seems to be very important is what happens to these patients afterwards. That is not determined when they leave the hospital. What I contend is that there are a large number of patients in whom sterility follows curettement of the placental site. That condition does not exist if the uterus is allowed to empty itself of the products of conception.

DR. N. S. HEANEY.—A point I wish to stress is, that habitual abortions are not always due to difficulty with the ovum or the corpus luteum, that sometimes there is an injury to the cervix due to a past delivery, abortion, or operation. I like to examine patients while they are aborting, for then the cervix is dilated and it can be entered, palpated, and inspected, and its integrity or injury definitely established, while if the patient is examined weeks later through the undilated cervix, the diagnosis is often doubtful. In such cases also the loose, soft, dilated tissues can be drawn together easily and a better repair insured than if the patient is treated "conservatively" during the act of abortion and examination and repair made after her convalescence.

DR. MARK T. GOLDSTINE.—I think the pulse is much more of an indicator of what is going on than the temperature. The pulse is much more subject to change; even though the temperature is normal for five days and if the patient still has a rapid pulse I believe it is a contraindication to go ahead with the operation. Many of our patients with the worst septic abortions die with subnormal temperatures but with a very high pulse rate.

DR. GALLOWAY (closing).—I agree with Dr. Hillis that a second invasion of the uterus is very dangerous. It is a rule in all surgery that a second procedure is more dangerous than the first. If we can do everything at the first sitting, we must do it. Packing the uterus is much deplored, but we feel that if the uterus is packed in the clean case, it helps to clean it up and it helps to save the occasional bleeding that would occur if it were not packed. We cannot see, from our figures, that packing causes any harm. Dr. Hillis' figures seem to me to indicate that the ratio of abortions in the Cook County Hospital is very high, as I suppose it naturally would be.

Dr. Browne's figures are not comparable to the figures in private practice. I agree that rectal examination is the only type that should be made. We do the Friedman test quite often. We have not much confidence in the dead fetus reaction. It must be remembered that the Friedman test costs the patient six dollars, and there has to be a definite indication for it before she is required to spend that amount.

Dr. Priest's figures run quite like ours, 201 out of 270 threatened incomplete abortions were curetted.

Our paper is not complete, especially as to treatment. When Dr. Woodruff mentioned thyroid extract, he is quite right. We use all methods. We try everything to prevent abortion. I think our figures in private practice bear this out. If we only list one in twenty in early pregnancy, it compares very favorably with the figures of the country as a whole. I think we have erred in the past in not doing more transfusions.

As Dr. Jones remarked, I would also like to emphasize that although we seem to have a high operative incidence, we do all that we can to save the pregnancy. It is to our advantage to have a child instead of an abortion. We think if you allow a patient to go too long in an attempt to empty her own uterus, it will not be long before she is infected. We think that by emptying the uterus early there is much less chance of having infection. Perforation does occur but it is rare.

I think Dr. Heaney's remarks about cervical repair are well taken. I have seen patients abort that would not have aborted if they had been taken care of from a gynecologic standpoint before they became pregnant. If we see a patient in that condition, we should stress the fact to her that she is liable to abort unless she puts herself in condition before she becomes pregnant again.

STUDIES ON RECONSTRUCTION OF THE FALLOPIAN TUBE*

Preliminary Report of an Original Technique

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OF THE many causes of sterility in the human female, tubal obstruction is the outstanding one that lends itself to surgical intervention. The number of methods devised and employed are far too numerous and diverse to be considered at this time. Since Martin[1] and Schroeder attempted the first recorded plastic operations in 1885, interest in this type of surgery has been more or less sporadic until recently. During these past few years, the various techniques have been modified and perfected to the point where the sum total of end results is fairly good, but certainly not satisfactory. For example, Greenhill,[2] as a result of a recent questionnaire sent to most of the outstanding gynecologists of this country, states that plastic operations for the relief of tubal obstruction result in 4.4 per cent pregnancies and 2.2 per cent live term babies. While the percentage of patent tubes resulting from such operations is undoubtedly much greater, and while results in individual clinics that specialize in this type of surgery are much better, the sum total of the results still leaves much to be desired.

The methods most commonly employed today for the surgical relief of tubal obstruction may be summarized as follows:

1. The so-called "circumcision" operation, in which the closed fimbriated extremity of a tube is amputated, the mucosa being cuffed back over the distal portion of the serosa.

2. The implantation operation. In this procedure the tube is divided distal to the point of obstruction and the proximal portion of the tube which contains the point of obstruction is sacrificed by excision. The proximal end of the patent portion of the tube is then passed through an opening in the uterine cornua made either by coning out or by incision, so that it again establishes a passage connecting the uterine and peritoneal cavities.

3. The various modifications of Estes' transplantation of an ovary into a cornual incision which opens into the uterine cavity.

4. A little used procedure is that of excision of the point of obstruction, with subsequent end-to-end anastomosis of the cut ends of the tube.

There seem to be two outstanding reasons for the failures which follow the use of these procedures, assuming that other factors are favorable to conception. The first of these is postoperative closure of the tube, due either to the formation of adhesions within the lumen of the tube, or to adhesions between the fimbriated end and some

*Read, by invitation, at a meeting of the New York Obstetrical Society, February 14, 1939.

This study was aided by a grant from the Commonwealth Fund of New York.

adjacent structure. The second reason is the failure of an ovum to reach the tubal ostium. This latter reason has gained considerable importance in view of the recent work of Westman,[3] who has clearly demonstrated that the normally functioning Fallopian tube applies itself to the ovarian surface at the time of ovulation in its quest of an expelled ovum.

With these facts in mind, it can be seen that any operative procedure which results in a material shortening of the Fallopian tube will definitely interfere with its function. Thus, if any portion of a tube is sacrificed, the fimbriated end will be withdrawn a corresponding distance away from the ovary, and the delivery of an ovum into the tubal ostium will become considerably less likely. As the length of the extirpated tubal sector is increased, the probability of an ovum finding its way into the tube is correspondingly decreased. If the point of obstruction in such a case is found to lie in the outer half of the tube, and such a tube is reconstructed by the implantation technique, nothing more than a fimbriated stump is left protruding into the peritoneal cavity.

The same basic principles apply to the "circumcision" operation, for here the length of the tube is decreased by the amount of the tube amputated, plus the length of the mucosal cuff which is turned back over the serosa.

In an effort to partially overcome this marked shortening of the tube as a result of operation, we performed a number of end-to-end anastomoses in *Macacus rhesus* monkeys, using bone wax, chromic catgut, and plain catgut in the tubal lumen to preserve its continuity. None of these substances was satisfactory, due to failure of absorption, inflammatory reaction, or focal constriction of the tube at the site of anastomosis. In addition to these objections, it was also found that extensive peritubal adhesions occurred in every case. It was thought that these resulted from digital and instrumental manipulation of the tubes during the operation.

At about this time, a substance became available which seemed to hold considerable promise, namely, prepared sheets of allantoic membrane, which are tough and easy to handle, yet offer a maximum amount of pliability. This material was found to cause a minimum amount of inflammatory reaction, as will be demonstrated later. Bearing these advantages in mind, two surgical procedures were devised which allowed of its use in the reconstruction of tubes which were obstructed either at the fimbriated extremity or along the course of the extrauterine portion.

The fimbriated end type of obstruction was duplicated as nearly as possible by traumatizing and closing the ends of the tube several weeks before the repair was to be carried out. When subsequently repaired, one tube was circumcised and cuffed according to the technique described by Holden and Sovak,[4] and others, while the opposite tube was treated in the manner to be described below. The end-to-end type of anastomosis was carried out upon normal tubes, no effort being made to produce an antecedent obstruction.

OPERATIVE PROCEDURE

An especially devised sheath of the Lindeman type (Fig. 1), the end of which had been ground to a round dull point was gently manipulated down the lumen of the tube for approximately 2 cm., after which the two inner trocars were removed. A long, fine, straight needle (Fig. 1), with 0000 chromic catgut attached was then passed through this sheath and out through the tubal wall, close to the mesosalpinx. With this piece of catgut in place, and protruding from the end of the tube, the sheath was removed. A sheet of allantoic membrane 4 by 6 inches was then gathered in the center in the same way one would pick up the center of a handkerchief. About this central point was tied the end of the suture which protruded from the fimbriated end of the tube. The fimbriated end of the tube was then gently held with gauze covered fingertips, while gentle traction was exerted upon the needle end of the suture, resulting in the passage into the lumen of the tube of a considerable

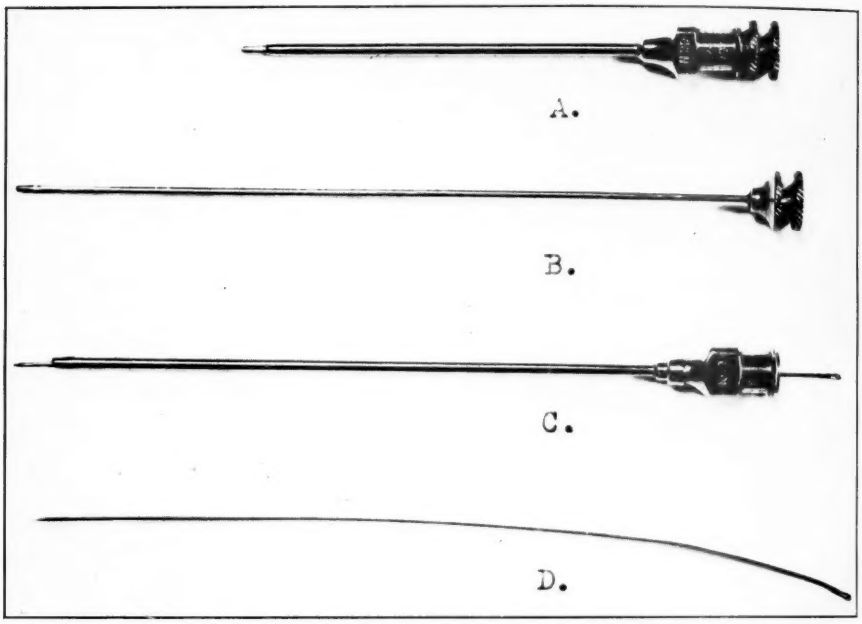

Fig. 1.—(*A*) Assembled short sheath and trocar for use in fimbriated end obstructions. (*B*) Long trocar to fit in (*C*). (*C*) Long sheath with needle inserted. (*D*) Flexible type of needle employed.

portion of the allantoic membrane. The remaining portion of the membrane protruded in a loose, pliable mass from the fimbriated end. This portion was then spread outward and downward over the serosa of the tube in such a manner as one would close an umbrella upon the handle. This resulted in the membrane completely covering the raw orifice of the tube, and at the same time protecting the distal portion of the tube against the formation of adhesions to surrounding structures. The various corners of the free edge of this membrane were then attached to the serosa of the tube and to the surface of the mesosalpinx with fine catgut, in order to hold it in place. The suture which had been placed through the tubal wall was likewise attached to prevent extrusion of the membrane due to tubal peristalsis. This procedure is outlined by steps in Fig. 2.

The experimental operation which was carried out in an attempt to determine the results which might be obtained in cases of isthmal obstruction, was as follows:

A ½ cm. segment of the middle of the tube was excised in the same way one would excise a point of obstruction in the Fallopian tube of the human being. A special sheath (Fig. 1) was then passed into the fimbriated end of the tube, through

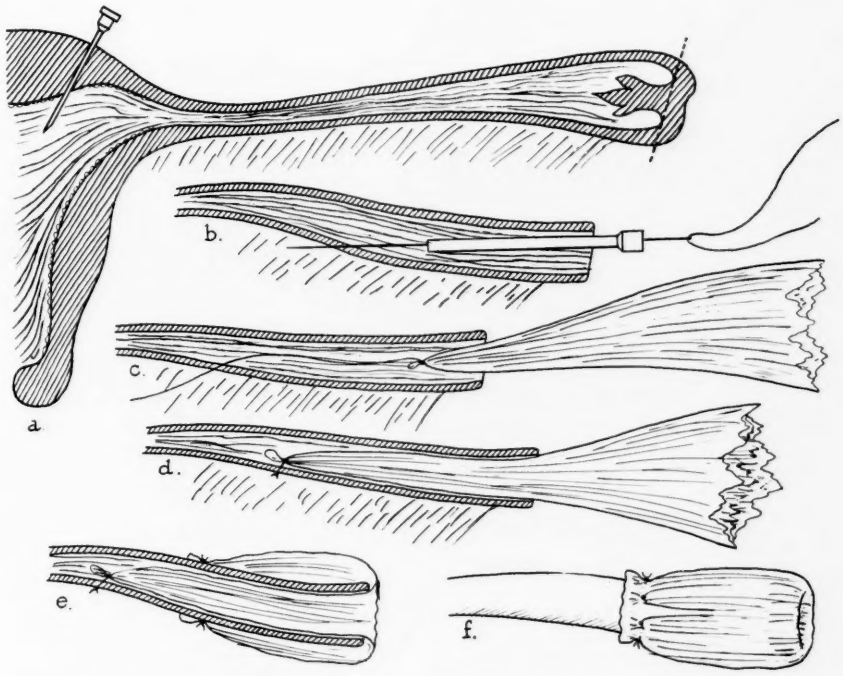

Fig. 2.—Steps of operative procedure employed for fimbriated extremity obstruction.

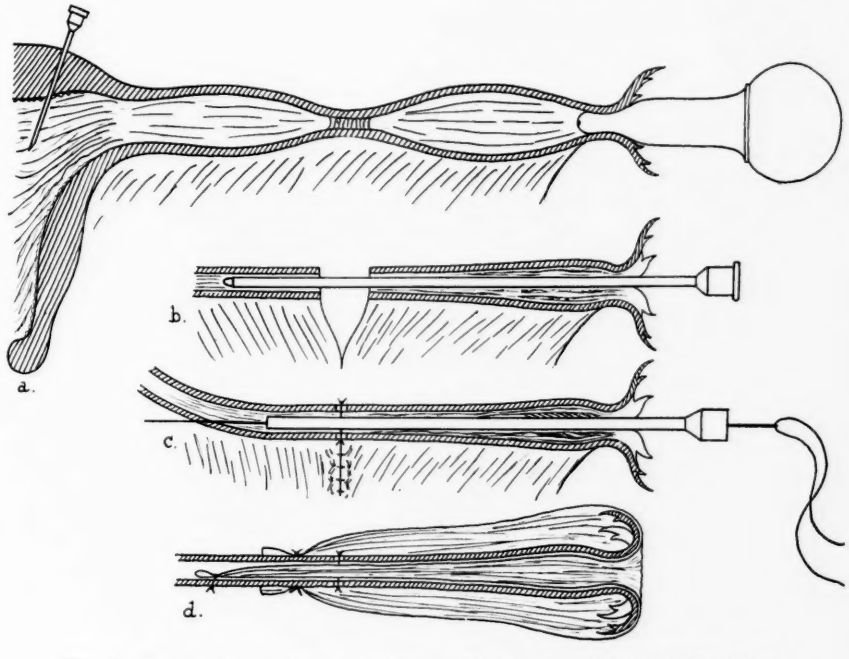

Fig. 3.—Steps of operative procedure employed for midpoint obstructions.

the lumen of the distal segment of the tube, and into the lumen of the proximal segment of the tube for a distance of about 1 cm. The needle with catgut attached was then passed through the sheath in the same manner as previously described. The two portions of the tube were then anastomosed end-to-end by the use of 0000 chromic catgut sutures which were passed through the serosa, muscularis, and mucosa. This procedure is outlined in Fig. 3. The sheath was then withdrawn and the allantoic membrane pulled through the distal lumen and into the proximal lumen in the same way as described for the previous operation. If the protruding portion of membrane was not sufficiently long to cover the point of anastomosis, another piece was sewed in place over this area. Before the abdomen was closed, a small amount of amfetin, or concentrated bovine amniotic fluid, was introduced into the peritoneal cavity to help prevent formation of postoperative adhesions.

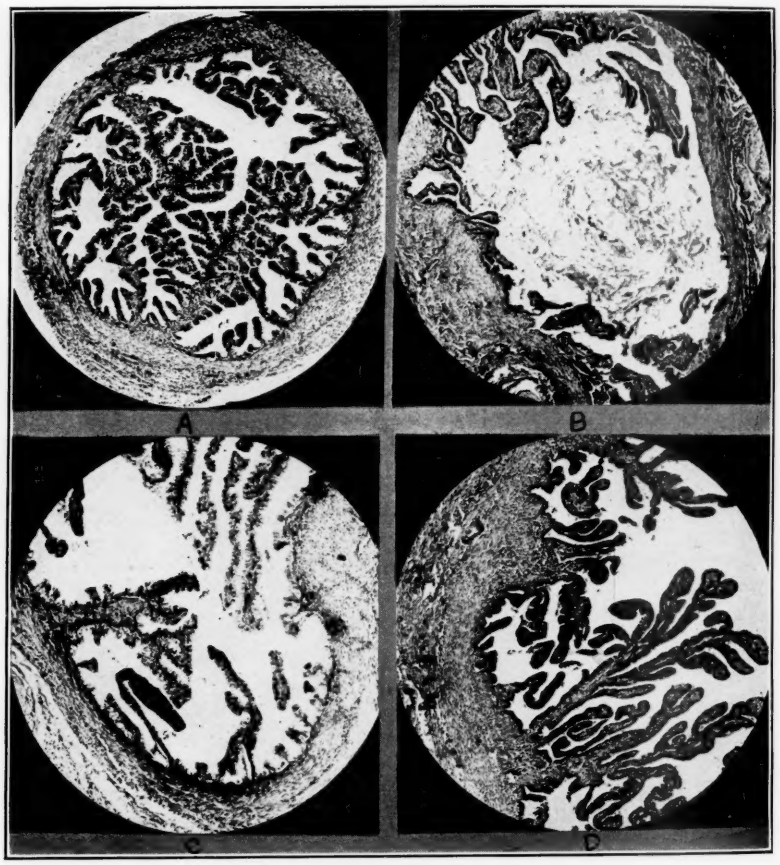

Fig. 4.—(*A*) Normal tube of *Macacus rhesus* monkey. (*B*) 6 weeks after introduction of bone wax into lumen. (*C*) 6 weeks after introduction of plain catgut. (*D*) 6 weeks after introduction of chromic catgut.

RESULTS

The operated tubes were removed at varying intervals following operation and studied carefully to determine the relative amount of inflammatory reaction which followed the use of the various substances.

Fig. 4(*A*) is a cross section of a normal Fallopian tube of a *Macacus rhesus* monkey.

Fig. 4(*B*) is a cross section of a similar tube six weeks after the introduction of bone wax into the tubal lumen. It will be noted that a considerable portion of the bone wax is still present.

Fig. 4(*C*) is a cross section of a similar tube six weeks after the introduction of plain catgut.

Fig. 4(*D*) is a cross section of a similar tube six weeks after the introduction of chromic catgut.

Fig. 5(*A*) is a cross section of a similar tube six weeks following operation and the introduction of chromicized allantoic membrane.

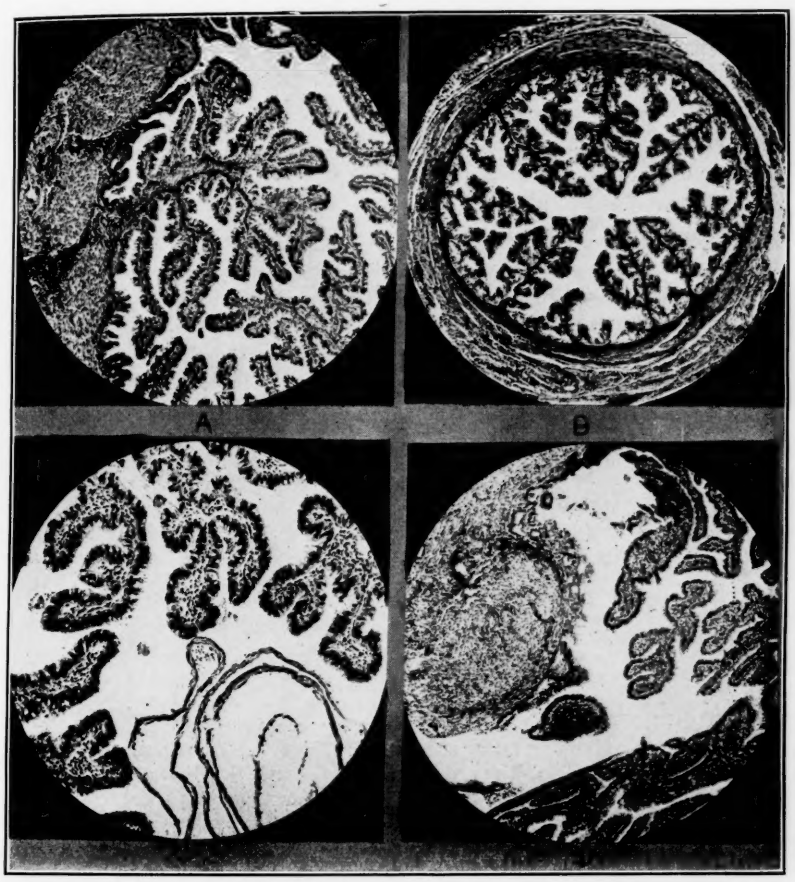

Fig. 5.—(*A*) Tube of *Macacus rhesus* monkey six weeks after introduction of allantoic membrane. (*B*) Similar tube after eighteen days. (Low power.) (*C*) Similar tube after fourteen days, showing allantoic membrane in lumen. (High power.) (*D*) Site of end-to-end anastomosis, six weeks after operation. (High power.)

Fig. 5(*B*) is a cross section of a similar tube eighteen days after the introduction of allantoic membrane.

Fig. 5(*C*) is a cross section of a similar tube fourteen days after operation and the introduction of allantoic membrane. This section demonstrates clearly the lack of inflammatory reaction to the allantoic membrane which may be seen to be still present in the tubal lumen.

Fig. 5(*D*) is a longitudinal section cut through the point of anastomosis in a similar tube, which had been subjected to an end-to-end anastomosis six weeks previous to removal of the tube.

These sections demonstrate clearly that chromic catgut causes far less inflammatory reaction and coagulation of the folds of the tubal mucosa than does either plain catgut or bone wax. It is also evident that the closest approach to the normal unoperated appearance of the tube is obtained by the use of allantoic membrane within the lumen. Section 5(*D*) shows that the amount of scar tissue produced as a result of the end-to-end anastomosis is not excessive and probably would not offer any appreciable obstruction to the passage of an ovum, since there is so little relative decrease in the tubal lumen.

CONCLUSIONS

All operations in which these two procedures were carried out resulted in tubal patency, with few if any adhesions about the field of operation.

However, evaluation of this technique is difficult on the basis of the work here reported, for it has been carried out, with few exceptions, upon the normal tubes of *Macacus rhesus* monkeys. While this allowed of more critical examination of the physical results than would have been possible in the human being, it must be borne in mind that many observers have come to grief through predicating human reaction upon animal experimentation. While realizing fully then that the diseased human Fallopian tube presents a number of barriers to success that are not encountered in experimental animals, it is believed that the procedure described above will result in far better end results than those which have previously been reported.

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DISCUSSION

DR. FREDERICK C. HOLDEN.—During my early days at Bellevue Hospital, we tried many procedures for the purpose of conserving menstrual function when operating for pelvic inflammatory disease. We found the Estes operation to be most satisfactory in cases when bilateral salpingectomy and partial oophorectomy were indicated. It is technically easy to learn and gives good physiologic results.

DR. I. C. RUBIN.—My personal experiences with ovarian implantation have not been successful. I have done the Estes operation on two patients and have done several implantations of the ovary by the Touffier method. I have had one doubtful pregnancy following the introduction of one of the poles of an ovary into the uterine cavity, ending in abortion. That, of course, I do not consider a successful case.

Dr. Gepfert's contribution is extremely ingenious. What it is going to turn out to be is difficult to say. He was dealing with practically normal tubes in a monkey whose rehabilitative and regenerative powers and resistance are far greater than those which any human female possesses. There is, besides, the factor of the pathologic situation which we meet with in the human subject. Dr. Gepfert has however shown that the allantoic membrane is valuable for the purpose of keeping the ostium or new stoma patent.

I would like to suggest that for the test of tubal patency in the monkey, which I think is important, he can employ the clinical method of insufflation if he will simply split the cervix laterally and so dispose of the obstruction offered by the

colliculus, a method which Dr. Morse and I have reported. I think he will get information more in that way than by resorting to the needle puncture of the uterus to insufflate the tubes.

DR. FRANCIS W. SOVAK.—There are one or two points that I want to discuss in connection with Dr. Gepfert's presentation: First, it is very unusual to meet with an obstruction at the site Dr. Gepfert has worked on. If you have an obstruction 2 or 3 cm. from the cornual portion of the tube, you are almost certain to have one also in the interstitial portion. Second, it is known to all of us that for reconstruction of a long, narrow viscus an end-to-end anastomosis is rather difficult and is likely to leave partial obstruction due to scar tissue.

I think he is wrong in stating that we are shortening the tube by the implantation operations. We have all seen inflamed tubes which are much longer than the normal tubes. In one case where pregnancy followed bilateral implantation, I was able at a subsequent operation to visualize the operative field and found that these tubes were not much shorter than the normal ones. I think that the alantoic membrane for the fimbriated extremity in association with the cuff operation will prove of value.

DR. BENJAMIN P. WATSON.—It has always seemed to me that the Estes is a bad operation. It has been difficult for me to conceive how an ovum, liberated from the ovary directly into the uterine cavity and there presumably immediately fertilized, can ever be implanted in the uterus. The ovum usually is fertilized at the outer end of the tube and it undergoes its first development during the passage down the tube into the uterus and it can only become implanted into the uterus after it has reached that stage of development. It, therefore, seems to me a very extraordinary thing if an ovum fertilized in the uterine cavity can stay there long enough, those necessary six or seven days, before it actually implants there.

The other objection, of course, is that only a very small pole of the ovary can possibly discharge an ovum into the uterus and the follicle that is ripening may be altogether distant from that small point of entry into the uterus. Consequently, it seems to me that the solution of this problem must lie in a proper reconstruction of a tube and of a tube of sufficient length to permit time for the ovum to develop during its passage down before coming into the uterus.

DR. WILLIAM H. CARY.—I recall that in 1927 I had occasion to review all the literature on this subject. If my recollection is correct, there was an unfortunately large number of complications following Estes' work, and I think Dr. Gepfert has said that the percentage of successes is 2.4. Is that correct?

DR. FRANCIS W. SOVAK.—In answer to Dr. Watson may I report actual experiences. When we first attempted the modification of the Estes operation with the use of our reamer, we had six bilateral cases. Of those six, 4 became pregnant. Three of the patients subjected themselves to an induced abortion for economic reasons, but we recovered the products of gestation on the ward. The fourth patient aborted spontaneously and in her case we also recovered the products of gestation.

DR. GEPFERT (closing).—There were 2.2 per cent successful deliveries, but 4.4 per cent of pregnancies. Some recent work shows that the use of certain endocrine substances stimulates regeneration of the tubal mucosa. By using these substances, we hope to obtain a complete regeneration of the tubal mucosa before the allantoic membrane has been absorbed. This may eliminate a large part of the scar tissue resulting from the end-to-end anastomosis.

The source of the allantoic membrane is interesting. As the cow approaches term, the allantois, a sac between the amnion and the chorion, contains from 8 to 16½ liters of fluid, and is a prolific source of allantoic membrane for the purposes we have described here.

Although the report today was on experimental work, we have done four human cases. The postoperative results are not known, due to the fact that all were done

recently. The operation itself is not difficult but is, of course, time consuming. The use of small instruments is absolutely essential.

For those who are interested I may say that the allantoic membrane is made by Lewis and Co., manufacturers of Curity catgut. It is contained in tubes and is obtainable in sheets 3 by 4, 4 by 6, and 6 by 8 inches in size. They have two products: one is plain and the other is chromicized. I strongly advise against the use of the unchromicized product because it produces a much more marked inflammatory reaction than does the chromicized.

THE TREATMENT OF DYSMENORRHEA WITH TESTOSTERONE PROPIONATE*

The Biologic Effects of Testosterone Propionate in the Sexually Mature Woman

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(From the Gynecological Service and the Laboratories of The Mt. Sinai Hospital)

THE subject of dysmenorrhea has engaged the attention of numerous investigators and an extensive literature has accumulated on the subject. The etiology of this distressing condition, however, is still obscure and its treatment still unsatisfactory. Reviews of the various hormonal theories of the cause of dysmenorrhea have recently been published by several authors.[1-4] Briefly, there are three current theories as regards the etiology of dysmenorrhea: (a) Deficiency in progesterone, permitting of the unopposed action of estrogenic hormone upon the uterine muscle; (b) excessive estrogen production resulting in hypermotility of the uterine musculature; and (c) excessive progesterone activity.[5] None of these theories is, however, adequately supported by controlled experimental studies.

The present communication deals with the treatment of dysmenorrhea with male hormone (testosterone propionate). The rationale for this form of therapy is based on the observation that testosterone counteracts certain of the physiologic effects of the estrogens in animals and human beings.

Ihrke and D'Amour[6] have shown that extracts of bull testes suppress estrus in rats. Similar results were obtained with testosterone by Robson[7] in mice and Browman[8] in rats. Zuckerman[9] has shown that in monkeys testosterone propionate inhibits follicle maturation and luteinization, resulting in suppression of the menses. Hartman[10] reported somewhat similar observations in monkeys. Recent experimental studies with testosterone in human females indicate that testosterone, if given in adequate dosage, suppresses the characteristic progesterone effect in the premenstrual endometrium and inhibits the usual proliferative phenomena so that the endometrium is reduced to a state of hypoplasia or atrophy;[11] causes regression in the vaginal smear[12, 13] and diminution of the glycogen content of the desquamated epithelial cells to a degree witnessed only in advanced estrogen deficiency (postmenopause or castration);[13] suppresses menstruation[11-14, 27] and inhibits the contractions of the uterus in rabbits[15, 16] and of the Fallopian tubes in women.[17]

*Read at a meeting of the New York Obstetrical Society, December 13, 1938.

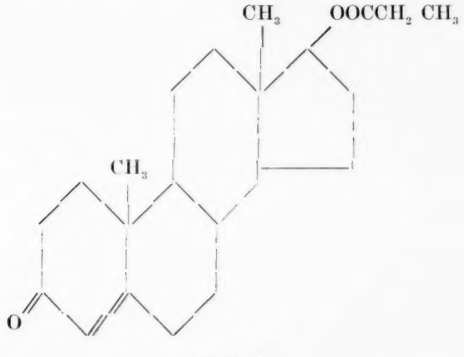
†Joseph Brettauer Fellow in Gynecology.

All of these phenomena indicate an antagonism between the female sex hormones (estrogens) and the male hormones (androgens). Furthermore, it has been known for some time that androgens are excreted in the urine by normal mature women. The role of the male hormones in the endocrine metabolism of the female assumes further significance in the light of the recent androgen studies reported by Koch and his co-workers.[18, 19] These studies have shown that normal, young women excrete daily an average of 26 international units of androgenic substance, as compared with an average of 40 units per day by men of similar age. It is noteworthy also that only traces of androgenic hormone (0.8 to 2.0 international units per liter) are excreted by girls before puberty. These observations warrant the assumption that androgens are intimately involved in the cyclical phenomena associated with normal menstruation. This suggested the possibility that dysmenorrhea might be due to an androgen deficiency resulting in the unopposed action of the ovarian hormones; and led to the use of an androgenic hormone (testosterone propionate) in the treatment of dysmenorrhea.

PROCEDURE

The present study was conducted on a series of 30 patients, whose ages varied from 15 to 45 years. Seventeen patients were under 30 years of age; 10 patients between 30 and 40; 3 patients were over 40 years of age. In all but 5 cases, the dysmenorrhea had been present since puberty. Twenty-seven of the patients had no palpable evidence of pelvic disease; 2 had suggestive signs of chronic adnexitis; one had several small myomas. Nineteen of the patients had normal, regular menstrual cycles; 11 had various degrees of menorrhagia.

In order to determine the presence or absence of normal progesterone activity and also to evaluate objectively the effect of the administered hormone, endometrial biopsies and vaginal smear studies were performed prior to and during the course of treatment. The endometrial biopsies were obtained with a suction curette. Vaginal smears were prepared according to the technique previously described.[20] The androgen selected for this study was crystalline testosterone propionate* (oreton, Schering; perandren, Ciba) which has been shown to be the most effective male hormone preparation.[21] The structural formula of testosterone propionate is:



DOSAGE

The testosterone propionate was administered intramuscularly in the gluteal region 3 times weekly in individual doses of 10 to 50 mg. per c.c. of sesame oil. In

*For the testosterone propionate used in this investigation, we are indebted to Drs. Stragnell, Schwenk and Gilbert of the Schering Corporation, Bloomfield, N. J. and to Mr. R. Mautner of Ciba Pharmaceutical Products, Summit, N. J.

some of the cases injections were given throughout the entire month, in several, only during the first week of the cycle and, in others, treatment was started on the fifteenth or sixteenth day of the cycle and continued up to the onset of the following menstrual period. The majority of the patients were treated during 3 successive cycles. The dosage of testosterone propionate was varied in different cases from 50 to 900 mg. per month. The total dosage varied from 100 to 1,500 mg. This wide variation in the amount of hormone administered occurred because of the uncertainty, in the early part of the investigation, as to the optimal dosage.

TABLE I

Results of Treatment of 30 Cases

Satisfactory results	26 cases
Complete relief	22 cases
Incomplete relief	4 cases
Failures	4 cases
Follow-Up on 25 Cases	
Symptom-free from 3 to 24 months after cessation of treatment	14 cases
Slight recurrence of pain after 2 months	8 cases

RESULTS

Satisfactory clinical results occurred during the course of treatment in 26 of the 30 cases (Table I). Twenty-two cases had complete relief; 4 were considerably improved; and in 4 cases there was no improvement. Following the discontinuation of treatment, 17 patients remained symptom-free during the period of observation which varied from three to twenty-four months. Ten of these have been observed for more than six months. In 8 cases there was slight recurrence of the pain within two months after discontinuation of the testosterone. In one patient there was a complete recurrence of the pain one month after the last injection.

In 9 cases 1 or 2 menstrual periods were suppressed during the course of treatment. Subsequent periods occurred with customary regularity. It is interesting to note that the menstrual bleeding which occurred in the menorrhagia group was appreciably reduced. A slight but definite decrease in the amount of bleeding occurred also in 10 patients of the normally menstruating group during the course of treatment. In 2 cases during the course of treatment, menstruation occurred five and ten days early. After discontinuation of the testosterone, a regular cycle was established.

ANALYSIS OF THE FAILURES

Of the 4 patients who failed to respond to the testosterone, 1 had uterine myomas; 1 probably had chronic adnexitis; the remaining 2 exhibited no palpable signs of pelvic disease. The dosage of testosterone used in these cases was comparable to that given the successful cases. That the failure to relieve the pain was not due to insufficient testosterone was indicated by the fact that in 3 of the patients a menstrual period was suppressed and in the remaining one delayed. All of these patients exhibited regressive changes in the vaginal smears. The failure in 2 cases may possibly be explained by the presence of organic disease.

ENDOMETRIAL BIOPSY STUDIES

In all of the 12 cases in which premenstrual biopsies were taken before treatment was begun, a secretory endometrium was found (Fig. 1). In 6 cases, endometrial biopsies were obtained during and after the course of treatment. The number of endometrial biopsies obtained in each case varied from 2 to 6. The endometrial biopsies obtained after testosterone administration, in all of these cases, revealed an absence of the secretory phase (Fig. 2), indicating a suppression or inactivation of progesterone. In addition, the endometrium in some cases showed some degree of hypoplasia, indicative of diminished estrogen effect (Fig. 3). Endometrial biopsies

performed before the next period (3 to 5 weeks after discontinuation of treatment) revealed normal secretory changes, indicating a restoration of a normal estrogen-progesterone relationship. In these cases the dosage of testosterone propionate varied from 500 to 900 mg.

Fig. 1.—Case H. L., aged twenty-four years, gravida i, para i. Premenstrual biopsy (taken before testosterone propionate), showing secretory endometrium. Menstruation began six days later with severe pain.

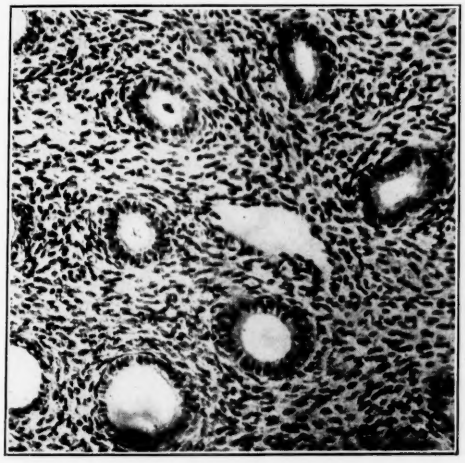


Fig. 2.—Case H. L. Premenstrual endometrial biopsy after 225 mg. testosterone propionate had been given during the preceding twenty-six days. Note absence of secretory phase. Uterine bleeding began the following day, lasting six days without pain.

VAGINAL SMEAR STUDIES

Smear studies were done in 24 cases. Preliminary smear studies revealed normal estrogen effect in all (Fig. 4). Following the administration of testosterone propionate, some cases showed regressive changes in the vaginal smears, as indicated by the appearance of variable numbers of "atrophy cells" and leucocytes (Fig. 4). The dosage administered to these cases manifesting regressive changes varied from 350 to 900 mg. of testosterone propionate. The smears remained in the regressive stage (estrogen deficiency) for periods varying from one to three weeks and thereafter showed signs of gradual recovery manifested by the return of large numbers

of squamous epithelial cells and the disappearance of the leucocytes and small atrophy cells (Fig. 6). In 7 cases in which the dysmenorrhea was relieved, the smears did not exhibit any evidence of regression either during the course of treatment or during the following month. Apparently a satisfactory clinical result can be achieved with doses of testosterone propionate that are smaller than are required to produce the regressive changes in the vaginal smears.

SIDE EFFECTS OF TESTOSTERONE PROPIONATE

Testosterone propionate in some cases produced masculinizing effects which are worthy of note, viz., facial hirsutism (6 cases); hoarseness of the voice (8 cases); very slight enlargement of the clitoris (2 cases); atrophic vaginitis (4 cases). The hirsutism, for the most part, is confined to the upper lip and chin and consists of a

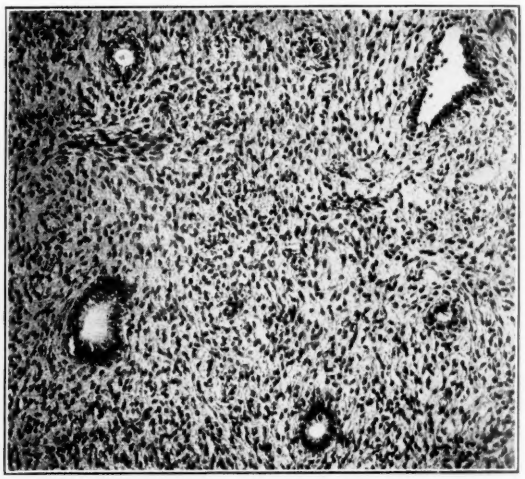


Fig. 3.—Case H. L. Endometrial biopsy after 800 mg. testosterone propionate given over a period of six weeks. Menstrual period suppressed. Biopsy taken two weeks after date of expected period. Note marked hypoplasia of the endometrium.

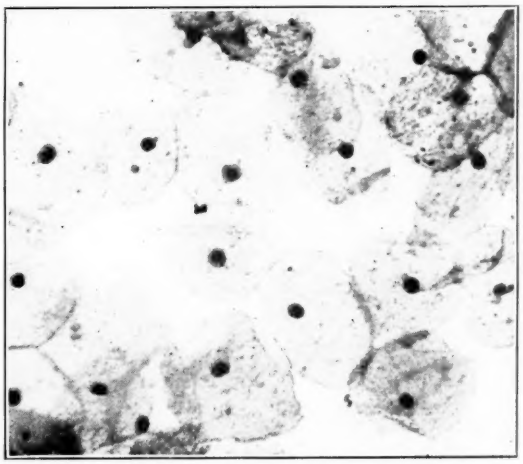


Fig. 4.—Case N. F., aged twenty-five years, gravida 0. Smear taken ten days premenstrually showing full estrogen effect (Reaction IV).

fine, downy growth. Brunettes with a natural tendency to hirsutism seem to be more susceptible. There is a gradual disappearance of the hair growth after discontinuation of the testosterone. In 4 of these cases the growth disappeared completely at the end of three months; in 2 cases a slight growth was still present at the end of four months. The hoarseness of the voice occurred before the hirsutism in 6 cases in which both were present. The patients usually attributed the changes in the quality of the voice to a cold. Examination of the larynx revealed diffuse congestion of the vocal cords. Following cessation of testosterone administration, improvement occurs progressively but slowly. At the end of six months there was still some slight hoarseness noticeable. In all of the patients in whom these effects were produced, the dosage exceeded 500 mg.

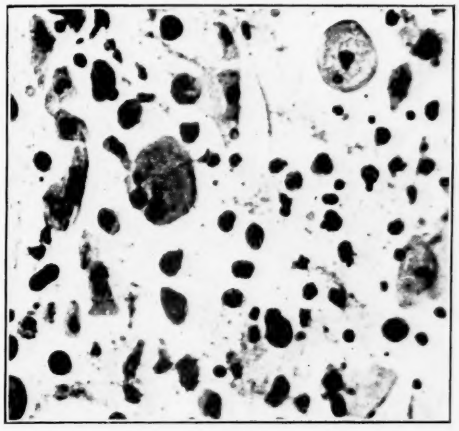


Fig. 5.—Case N. F. Smear showing marked estrogen deficiency (Reaction II) after 650 mg. testosterone propionate. Menstrual period suppressed. Smear was taken two weeks after date of expected period. Note "anisocytosis" and "poikilocytosis"; predominance of small epithelial cells ("atrophy cells"); scattering of leucocytes.

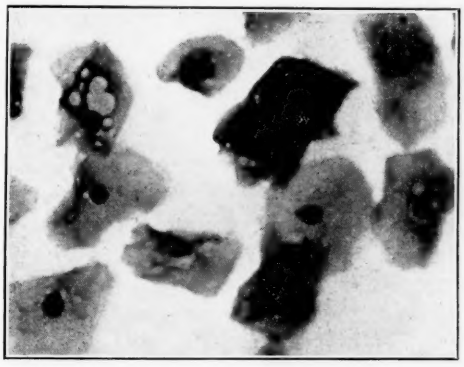


Fig. 6.—Case N. F. Smear taken twenty-six days after smear in Fig. 5. Note return of squamous epithelial cells; disappearance of "atrophy cells" and leucocytes. Definite estrogenic effect (Reaction III). Patient menstruated sixteen days later without pain.

Four of the patients complained of vaginal discharge which was found to be due to a vaginitis analogous to the senile type. Vaginal smears revealed the characteristics of advanced estrogen deficiency. The vaginitis subsides spontaneously within two to three weeks and is associated with a replacement of the "atrophy cells" in the smears by the large squamous epithelial cells, indicative of return of estrogen

activity. In the cases in which the vaginitis was bothersome, relief was obtained in a few days by the nightly use of vaginal suppositories containing 2,500 rat units of estradiol (progynon-DH).

DISCUSSION

The biologic effects of testosterone propionate in the sexually mature woman vary, depending upon the dosage as well as the time of the cycle when the hormone is administered. There appears, furthermore, to be considerable individual variation in the response to similar doses of testosterone. With doses of 200 mg. or less, menstruation was not affected (with the exception of 2 patients in whom menstruation occurred prematurely, five and ten days) and no objective changes were noted in either the endometrium or the vaginal smears. Three hundred milligrams or more given during the first ten days of the cycle may cause delay (from three to five days), diminution in the flow of the next period, and may suppress the normal progestational changes in the endometrium. Approximately similar doses given during the last 10 days of the cycle usually cause no delay in the period and no endometrial and vaginal smear changes during the current cycle.

If doses of 500 mg. or more are given during the first seven to ten days of the cycle, the next menstrual period may be delayed from two to six weeks. During the period of amenorrhea the endometrium shows absence of the secretory phase and various stages of subnormal proliferation. Premenstrual biopsies performed during succeeding cycles show a normal secretory endometrium. The vaginal smears during this period of temporary amenorrhea in all cases show advanced degrees of estrogen deficiency indicated by the predominance of leucocytes and atrophy cells with absence of cornified cells (Reaction I and II). In all of these cases evidence of return to a normal estrogen effect (disappearance of leucocytes and replacement of atrophy cells by squamous epithelial cells) was noted two to three weeks after the discontinuation of testosterone propionate.

It is apparent that striking undesirable effects, both clinical as well as morphologic, result from administering more than 500 mg. of testosterone propionate. This appears to be the approximate threshold of androgen tolerance in the human female. Fortunately, one can achieve satisfactory therapeutic results with smaller doses without inducing any of the undesirable effects noted above and without incurring any danger of subsequent interference with the normal menstrual phenomena.

It is interesting to note that one patient (not included in this series) missed a period after 600 mg. of testosterone propionate, developed a "negative" smear which persisted for two weeks, then began to return to normal. At the same time she developed slight hoarseness and facial hirsutes which gradually subsided. When the patient did not menstruate the following month, a pregnancy test was performed which was found to be positive. The patient had apparently conceived during the period of amenorrhea. She was delivered at term of a perfectly normal male baby, weighing 7 pounds 12 ounces.

We feel that the optimal dosage for the relief of dysmenorrhea is in the neighborhood of 250 to 350 mg. given in divided doses during one cycle. If the pain is relieved completely or partially with this dosage, it is advisable to give an additional course of therapy decreasing the amount by half. If only slight or no improvement is obtained, a second course should be given.

We have found that the vaginal smear serves as a sensitive indicator of androgen overdosage. Regressive changes in the smear occur several weeks before the clinical manifestations of androgen overdosage appear. Although we have not observed any of the undesirable androgenic effects with the dosage recommended, we wish to draw attention to the fact that there is some variation in the tolerance of different individuals to the hormone and suggest that vaginal smears be taken twice weekly to guard against the occurrence of the undesirable side effects in patients with subnormal tolerance. If the vaginal smears show evidence of estrogen deficiency (Reaction I or II), therapy should be discontinued. It is worthy of note that in many of the cases symptomatic relief was obtained with doses which were insufficient to produce regressive changes in the smears. In 4 cases symptomatic relief was obtained with less than 100 mg. The follow-up in these cases varied from four to sixteen months without recurrence of symptoms.

As we survey the results of this investigation, the question arises as to the modus operandi of the testosterone. The results of the present study seem to indicate that in the sexually mature human female testosterone propionate suppresses or counteracts the effects of the ovarian hormones (estrogen and progesterone). This is in agreement with the reports of suppression of estrus in animals following male hormone administration.[6-10] It should be pointed out, however, that recent studies have shown that testosterone propionate has a definite gonadotropic effect in immature female rats, resulting in follicle growth, corpora lutea formation and hypertrophy of the uterus and vagina.[22] The trophic effects on the uterus and vagina can be produced in spayed (as well as intact) both immature and mature rats.[23-25] These observations appear to indicate that in rats testosterone propionate has a gonadotropic effect (produced, probably, through the hypophysis) as well as a direct estrogen-like effect (demonstrated histologically) on the genital tract. In human beings and monkeys, on the contrary, the testosterone evidently has an inhibitory action opposing or negating the effect of the ovarian hormones. It is interesting, in this connection, to note that it has been shown that testosterone propionate suppresses the excessive gonadotropic hormone excretion in a human female castrate[26] and it seems not illogical to assume that a similar inhibition of the gonadotropic activity of the hypophysis may occur in women with regular menstrual cycles. This concept of the inhibitory action of testosterone upon the hypophysis is supported by the observation that administration of adequate amounts of testosterone propionate during the first week of the menstrual cycle (before the gonadotropic factors of the hypophysis have exerted their effect on the ovaries) results in suppression of the subsequent menstrual period, whereas

similar amounts of testosterone given during the last week of the cycle (after ovulation has occurred) have no effect on the following menstrual period. This theory, however, does not explain the rapid appearance of morphologic signs of advanced estrogen deficiency in the endometrium and vaginal smears following testosterone administration, since it is inconceivable that suppression of estrogen formation alone during one cycle would, by itself, be the cause of such striking regressive histologic changes. Signs of marked estrogen deficiency (Reaction I and II) were found as early as three weeks after testosterone was administered, whereas after surgical castration evidence of similar degrees of estrogen deprivation is not usually observed until many months have elapsed after removal of the ovaries. The rapidity with which such an advanced degree of histologic regression in the vaginal mucosa makes its appearance suggests that it is not solely the result of cessation of estrogen production but indicates that in addition there is also an actual inactivation of whatever estrogens are stored or circulating in the body.

It is tempting, in the light of the observed biologic effect of testosterone in women, to formulate a theory concerning the causation of functional dysmenorrhea. According to this theory, the androgens are conceived as playing an important role in the hormonal organization of the normally menstruating female, viz., to balance or modify the physiologic effects of the ovarian hormones. Dysmenorrhea is attributed to an androgen deficiency resulting in the unopposed or unmodified action of the ovarian hormones. The following evidence is offered in support of this theory: (a) androgens play an important part in the normal hormonal economy of the sexually mature female; (b) there is experimental evidence indicating a definite antagonism in the human female between estrogens and androgens; (c) 86 per cent of the cases of functional dysmenorrhea in this series were relieved when treated with a potent androgen (testosterone propionate). This theory awaits verification by quantitative studies of the androgen excretion in cases of functional dysmenorrhea.

The question arises as to the practical therapeutic value of testosterone propionate for functional dysmenorrhea. We realize that an accurate evaluation of clinical results in as complex a condition as dysmenorrhea is beset with difficulties. It is well-nigh impossible to exclude a psychic component from the therapeutic results obtained regardless of what form of therapy is employed. However, in this study an attempt was made, by the correlation of objective findings with the clinical results, to evaluate the therapeutic effect of the administered hormone per se. Although the results in this series have been very gratifying, we do not believe that testosterone is the complete answer to the problem of dysmenorrhea. We do feel, however, that testosterone is a valuable addition to our therapeutic armamentarium.

SUMMARY AND CONCLUSIONS

1. A group of 30 patients with dysmenorrhea was treated with testosterone propionate.

2. The biologic effects, clinical as well as morphologic, of testosterone propionate on the sexually mature human female are described.

3. The level of testosterone tolerance was established at approximately 500 mg.

4. Administration of upwards of 500 mg. resulted in the appearance, in some of the cases, of: (a) masculinization phenomena, viz., hoarseness of the voice, facial hirsutes, slight enlargement of the clitoris; and (b) evidence of estrogen deficiency, viz., suppression of menstruation, atrophic vaginitis, varying degrees of hypoplasia of the endometrium, and "negative" vaginal smears.

5. Normal cyclical phenomena (clinical and morphologic) returned spontaneously in all cases within two months after treatment.

6. With doses of 300 mg. or less neither androgenic nor estrogen deficiency effects were produced.

7. In the treatment of dysmenorrhea the dosage of testosterone propionate recommended is 250 to 350 mg. given during one cycle.

8. Symptomatic relief was achieved in 26 of the 30 cases.

9. The suggestion is made that the biologic effects of testosterone propionate (in doses of 500 mg. or more) in women is brought about by inhibition of the gonadotropic factors of the hypophysis with consequent suppression of ovulation, estrogen and progesterone formation and menstruation, as well as by inactivation of the circulating estrogens and estrogen stores in the body.

10. The therapeutic effects noted with smaller doses of testosterone propionate are probably the result of partial inactivation or modification of the action of the estrogens and progesterone.

11. The theory is advanced that functional dysmenorrhea may be caused by an androgen deficiency.

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DISCUSSION

DR. SAMUEL H. GEIST.—This contribution represents a step in the investigation of the value of androgen therapy in functional gynecologic disease. We have already published some observations on the use of this agent in the treatment of certain types of metrorrhagia and menorrhagia where we obtained what we believe to be very suggestive and in some instances very satisfactory results.

In view of the fact that the normal woman excretes a definite amount of male hormone we cannot disregard its importance in her physiologic make-up. We feel that an investigation of the value of androgens in various types of endocrine diseases in the female might produce very helpful results in certain functional conditions that have been difficult to treat. They include metrorrhagia and menorrhagia and dysmenorrhea, and also some aspects of the menopause itself. Recently there have been some publications by French authors on the treatment of fibroids on an endocrinologic basis, with some very suggestive results.

The failures which we reported are in keeping with the treatment of dysmenorrhea by any method. They may be due to the fact that our dosage is insufficient. They may be due to the fact that the individual is resistant to the dose which we considered adequate, and what is much more important, they may be due to the fact that we used it in some cases of dysmenorrhea where there was no indication for its use.

Dysmenorrhea does not represent a single entity. On the contrary, it is a symptom-complex which often is associated with many etiologic factors and until we learn to classify it properly and recognize the various types there will naturally be a certain proportion of failures with any single method of treatment. We, of course, realize that the number of cases in this study is small and consequently definite conclusions cannot be drawn from them. We do not offer this form of therapy as a cure-all, but we think it is a very suggestive line of thought and a very encouraging line of therapy.

DR. HOWARD C. TAYLOR, JR.—This paper must be considered from two separate points of view: first, as a contribution to the physiology of the female reproductive system, and, second, as a possibly practical method of treating dysmenorrhea. From the first point of view the paper is unquestionably important. From the second, as is the case with all new contributions in the treatment of dysmenorrhea, one should withhold severe judgment.

From a pathologic standpoint this paper brings out certain points. In the first place, it corroborates experimental work in animals, showing that testosterone may prevent the effect of estrogenic and progestational substances on the endometrium and on the vagina, as indicated by the changes in the character of the endometrium and the vaginal smear. In the second place, testosterone is seen to have the ability in large enough doses to bring out the masculine qualities, such as changes in the voice, changes in the clitoris and the development of abnormal hair.

An important point which this paper seems to settle is the range of dosage that we will probably have to use when testosterone is administered. This is of fundamental value. The treatment with estrogenic hormone went through a period of years when the dosage was so small that there could have been no actual effect although we imagined the contrary. We may hope to skip this stage with testosterone, for we start with this report in which the substance has been given until it produced objective effects. We have been told that with less than 200 mg. menstruation is unaffected, while with a dosage of over 250 mg. there may be a temporary atrophy of the endometrium. In doses of over 500 mg. there may be some unlooked for results, such as masculinizing effects. The fact of having a dosage related to objective effects is going to be of great assistance to us in working out the therapy of this new drug.

As far as the practical application of this method to the treatment of dysmenorrhea is concerned one can raise certain questions. Any type of therapy will be followed by a certain percentage of cures in dysmenorrhea. Wilson presented before this Society a few days ago a paper on the treatment of dysmenorrhea with

progesterone and reported a fair percentage of cures, using somewhere between 2/25 and 6/25 of a rabbit unit. There have been numerous other reports in the literature in the last few years, of cure of dysmenorrhea with various types of endocrine therapy. One report (Lackner, Krohn and Soskin, AM. J. OBST. & GYNEC. 34: 248, 1937) showed 20 per cent of failures and another (Katz and Parker, AM. J. OBST. & GYNEC. 34: 38, 1937) only 2 per cent. This report which indicates 88 per cent of successes is excellent but it must bear the burden of contrast with previously undoubtedly over-optimistic figures.

The second point is the question whether these are temporary or permanent results. The cases have been observed over a relatively short period of time. It would be a most unexpected piece of good fortune, if the unwanted side effects, such as atrophy of the endometrium and the occasional masculinizing signs, should be temporary and the beneficial effects, such as the disappearance of the pain, should be permanent.

There is, finally, one question which, although it is at present largely theoretical, is perhaps the most important one. One must ask whether with this substance in large doses we are not making too vigorous an assault on the fundamental physiology of the reproductive tract. It is to be remembered that in these doses one delays menstruation, one produces an endometrium which is said to be atrophic, one inhibits ovulation and in only double the therapeutic dose one produces certain masculinizing changes. To substitute for dysmenorrhea a type of endometrium which is atrophic is not the elimination of the specific cause of dysmenorrhea. It is simply a complete alteration, almost a cessation, of the functions of the reproductive tract. If you x-ray the pelvis and produce amenorrhea, you stop the pain of menstruation but do not eliminate the cause of the dysmenorrhea. There is at least the possibility then that this chemical attack on the function of the ovary may be as fundamental as the use of radiation. This treatment should be accepted with a certain degree of caution especially in young women who are still to bear their children. Testosterone in doses of 250 mg. is something a little different from what we have usually been accustomed to in gynecologic endocrinology, because it does involve such fundamental alterations in the physiology of the ovary and uterus.

These are not to be construed as criticisms, but merely as questions that come to one's mind at this time. I am anxious that they should not detract from what I believe is a very important addition to our knowledge of the physiology of the reproductive tract, and perhaps a very important contribution to our knowledge of the therapy of dysmenorrhea.

DR. ALFRED C. BECK.—A number of years ago in our clinic we attempted to suppress menstruation by x-ray in the treatment of certain cases of inflammatory disease. Perhaps the suppression of menstruation did eliminate some obscure inflammatory disease which was responsible for the dysmenorrhea. Instead of using the x-ray in some of these inflammatory conditions, the use of male hormone might be tried.

DR. ROBERT WALTER.—It is important to note that the undesirable side effects, i.e., hypertrichosis, voice changes, suppression of menses, etc., did not occur in this series of cases when 250 mg. or less of testosterone propionate were used. However, to guard against overdosage it is advisable to do vaginal smears simultaneously with the administration of testosterone propionate and to discontinue therapy when smears indicative of estrogen deficiency appear.

DR. HOWARD E. LINDEMAN.—The presenters of the paper have pointed out a masculinizing effect produced by the male hormone. As so many of these cases of dysmenorrhea in young women are associated with sterility, the question arises whether this tendency towards masculinizing, even though the androgen be given in small doses, would not still further diminish fertility. I would like to ask whether the authors of this paper have any knowledge of pregnancy following this treatment.

DR. SALMON (closing).—I should like to point out that in this presentation two separate groups of facts are incorporated: (1) an attempt to determine the effect of testosterone on the adult, human female and (2) the effect of testosterone on functional dysmenorrhea. In order to determine the first, we experimented with dosages varying from 50 to 900 mg. per month. In our report, we have deliberately stressed the masculinization phenomena and the estrogen neutralizing effects of testosterone because they exemplified, in an exaggerated manner, the probable physiologic significance of androgens in the human female. Fortunately, it appears that there is a wide margin of safety between the therapeutic dose and the dosage required to produce estrogen deficiency symptoms or androgenic effects.

The problem of the mechanism of testosterone action in women is an intriguing and, in some of its aspects, at present, a baffling one. That inhibition of the gonadotropic activity of the hypophysis and consequent suppression of ovulation and menstruation occur as a result of administration of large doses of testosterone propionate seems proved. But what do we know about the mechanism of the masculinization phenomena? It seems that the testosterone, after inhibiting the hypophysis and inactivating the circulating estrogens or estrogen stores, stimulates some growth of hair on the face and coarsens the voice. Whether the testosterone produces these masculinizing effects directly or through the adrenal cortex is not clear. It seems likely, however, that the former is the more probable modus operandi. It is interesting, in this connection, to recall that Butler and Marrian recently isolated isoandrosterone (an androgen not far removed from testosterone) from the urine of a woman with adrenal virilism.

But what happens when doses that are too small to cause masculinizing effects or suppress menstruation are given? We suggest that in the normal mature female there is a balance between the androgens on the one hand and the estrogens and progesterone on the other and that when testosterone is given in dysmenorrhea it partially inactivates or, rather, modifies the action of the estrogens and progesterone. Our observation that not only functional dysmenorrhea but also some types of functional bleeding, premenstrual tension and premenstrual mastalgia can be relieved with testosterone propionate, suggests that in these conditions, too, the normal balance is upset because of a deficiency or abnormality in the androgen metabolism. I trust, however, that we have not created the impression that we have conclusive evidence to support this theory. Our evidence, I must confess, is entirely indirect, based on the changes in the vaginal smears and endometrium and on clinical observations. We are fully aware of the necessity of following these cases with androgen, estrogen, and pregnandiol excretion studies before we can prove our theory of androgen deficiency in functional dysmenorrhea.

If we look to animal experimentation for confirmation of our theory, we are met with a confusing array of paradoxical phenomena. As a matter of fact, some animal experiments indicate that testosterone actually has a stimulating effect on the genital tract, in some respects similar to that of the estrogens. Thus, if testosterone is given to immature, female rats, it produces opening of the vagina within seventy-two hours, follicle growth and corpora lutea in the ovaries, hypertrophy of the uterus and proliferation of the endometrium. The effects on the uterus and vagina occur in spayed, immature rats as well, indicating that the testosterone has a direct estrinlike effect on the Müllerian tract of rats as well as a gonadotropic effect upon the immature ovaries, the latter effect exercised through the hypophysis. Coincidentally, the preputial glands, which are the homologues of the prostate, are stimulated to a five- to eight-fold increase in size. We find, therefore, that giving male hormone to immature female rats produces not only precocious development of all the components of the female genital tract but also stimulates the vestigial male organs. With the present status of our knowledge, animal experimentation does not help us in our quest for an understanding of the mechanism of the testosterone action in the human female. We must content ourselves, for the time being, with the knowledge that testosterone is very closely related, chemically, to progesterone and corticosterone; that under normal conditions a significant amount of androgenic hormone is excreted by the adult female; that androgens probably play an important role in the metabolism of the steroid sex hormones of the human female; that

the adrenal cortex is in some manner probably involved in the metabolism of the androgens in the female; and that in some conditions, e.g., dysmenorrhea, functional bleeding, premenstrual tension and premenstrual mastalgia, administration of testosterone produces symptomatic relief.

In answer to Dr. Taylor's question concerning the possibility of inflicting some permanent damage upon the ovaries by giving testosterone, I wish to point out that the rapid recovery of the vaginal smear, the prompt restitution of the normal, proliferative and progestational endometrium, the return of a normal menstrual cycle and, in one case, a normal pregnancy, all seem to indicate that there is no danger of any lasting impairment of ovarian function. The question arises, however, as to whether the administration of the testosterone may not have some effect on the genitalia of some future offspring. In our case, the baby was a male with normal genitalia. I regret that we have no further factual evidence on this subject.

As regards the use of testosterone propionate for patients with pelvic inflammatory disease, with the objective in mind of suppressing menstruation, as suggested by Dr. Beck, I would say that on the basis of our observations this would not seem to hold forth much hope. In order to suppress menstruation for more than one month, one has to give enough hormone to bring the patient within the range of estrogen deficiency and masculinizing symptoms, which would militate seriously against the usefulness of such a procedure.

In reference to the question of the relationship of progesterone to dysmenorrhea, it is interesting that we have recently produced typical progestational endometrium in postmenopause women with a synthetic steroid (pregneninolone) closely related to both testosterone and progesterone. It is not, therefore, inconceivable that by giving testosterone propionate to patients with dysmenorrhea we may be paralleling some phase of the normal physiologic action of progesterone (or of some intermediate product of progesterone metabolism) which we do not, at present, recognize.

AN ANALYSIS OF 573 CASES OF TWIN PREGNANCY

II. The Hazards of Pregnancy Itself

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IN THE first paper of this series[1] the biologic aspects of 478 cases of human twinning were analyzed and the conclusion was reached that monozygotic (single ovum) and dizygotic (double ovum) twinning represent fundamentally different processes. Dizygotic twinning is specifically influenced by heredity, age, and parity; while monozygotic twinning appears to be mainly a chance phenomenon. In the next five papers we propose to analyze the clinical aspects of twinning. The present study concerns itself with the course of pregnancy. The four succeeding papers will consider labor, the puerperium, the newborn, and fetal and maternal mortality. In the seventh and final paper the placentas of twin gestations will be discussed.

The cases upon which this study (Paper II) is based occurred on the combined hospital and home delivery services of the Johns Hopkins Hospital from the inception of its obstetric department in 1896 to Oct. 1, 1938. Over 95 per cent of the patients were delivered on the ward service, which is almost equally divided between white and colored.

DIAGNOSIS BEFORE ONSET OF LABOR

In this portion of the investigation it is my purpose to determine the percentage of cases in which the diagnosis of twins was correctly made before the onset of labor and the percentage in which it was missed. This analysis is limited to patients who received prenatal care, unregistered emergency admissions being excluded. The material was further delimited by considering only viable twins born after Jan. 1, 1925, so that our figures might show what can be expected of modern diagnostic methods, aided in some instances by the x-ray.

As can be seen from Table I, either the diagnostic acumen displayed was of low order or the ante-partum diagnosis of twins frequently presents technical difficulties. The presence of the two infants was definitely recognized before the onset of labor in a little less than two-thirds of 225 viable twin pregnancies; and in more than one-fourth the condition was wholly unsuspected. There was the anticipated difference between premature and term twin pregnancies, in the latter the ante-partum diagnosis was made in 70 per cent and in the former in only about 50 per cent. Of 50 cases of twins reported by Dame Louise McIlroy,[2] 74 per cent were diagnosed ante partum. It is apparent that the obstetrician often neglects to think of the possibility of twins, for when seriously considered it is likely that a diagnosis of multiple pregnancy is rarely missed.

TABLE I

NUMBER OF CASES		DIAGNOSED		UNDIAGNOSED		SUSPECTED	
Term and premature	225	143	(64.4%)	65	(28.8%)	17	(6.8%)
Term	128	92	(71.8%)	24	(18.8%)	12	(9.4%)
Premature	97	51	(52.6%)	41	(42.2%)	5	(5.2%)

PROPORTION OF TERM, PREMATURE, AND ABORTION

At this point it is necessary to explain our use of the words: term, premature, and abortion. We have considered any twin pregnancy a term pregnancy if either of the two infants weighed 2,500 gm., and premature if each of them weighed less than 2,500 gm., but one weighed more than 1,500 gm. The conceptus was considered an abortion if both fetuses weighed less than 1,500 gm., unless one survived and in the five instances where this occurred the case was arbitrarily considered a premature gestation. Objection may well be made to this classification (as will be discussed in Paper V) on the basis that at the same period of conception the twin fetus probably weighs less than the single fetus, and therefore the usual standard weights for the classification of single fetuses should be reduced a few hundred grams when distinguishing mature from premature twins. However, since there is no reliable data for the weight of the forty weeks' or thirty-six weeks' twin fetus, we have been forced to use the weight differentiation ordinarily employed for the single fetus. We have

purposely disregarded the length of the fetus in defining term, premature, and abortion, since we feel this measurement is subject to too great error at the hands of inexperienced anthropometrists.

On the basis, then, of the single criterion of weight, 281 (49.0 per cent) of our 573 twin pregnancies were delivered at term, 222 (38.7 per cent) were delivered prematurely and 70 (12.3 per cent) were aborted. It is likely that the last figure (12.3 per cent) is less than the true percentage of twin pregnancies which actually terminate in abortion, for in the clientele from which our material is drawn a fair proportion of abortions must take place without the attendance of a hospital physician. Furthermore, especially when the abortion is associated with defective germ plasm, a second early embryo may go unobserved or unrecognized. Of the 503 viable pregnancies, 56 per cent resulted in term, and 44 per cent in premature infants. Using the one criterion of weight, Dr. C. H. Peckham in a study at the Johns Hopkins found that of 38,944 viable single births, 91 per cent resulted in fetuses of term weight (more than 2,500 gm.), and 9 per cent in premature infants (1,500-2,500 gm.). It is to be noted that in one and the same clinical material, infants of premature weight occurred with five times the frequency in twin births.

Dame McIlroy[2] states that 64 per cent of the twin pregnancies in her series went to term, 24 per cent terminated prematurely and 8 per cent were aborted. Unfortunately she does not define her standards of term and prematurity. Gernez and Omez[11] in reporting 236 twin pregnancies from Lille state that 67 per cent progressed beyond the beginning of the last month, 23 per cent terminated during the seventh and eighth months and 10 per cent were aborted.

There was a marked difference between primiparas and multiparas in respect to the weight of the twins at birth. Of 127 primiparas, 46 (36.2 per cent) had twins of term weight, 68 (53.5 per cent) premature, and 13 (10.3 per cent) abortions. Among 440 multiparas, 232 (52.7 per cent) had term fetuses, 153 (34.8 per cent) premature and 55 (12.5 per cent) abortions. This difference between primiparas and multiparas can be more strikingly demonstrated when we note that in only 40 per cent of the 114 primiparas who reached viability was either fetus of term size, in contrast to 60 per cent of 385 multiparas. In the following section on the duration of pregnancy it will be seen that there is no essential difference between the duration of twin pregnancy in the primiparous and multiparous woman. It is obvious therefore that the explanation must lie in the more rapid growth of the twin fetus born to the multiparous woman, per unit time of intrauterine existence. This observation is in keeping with Dr. C. H. Peckham's findings, that, in general, multiparas give birth to larger children than primiparas.

DURATION OF PREGNANCY

From the 480 pregnancies which terminated in term or premature twins, 247 were selected for an analysis of the duration of twin pregnancy. All cases in which labor was induced or elective cesarean sec-

tion performed were excluded. Likewise, all cases of syphilis were discarded, as well as those in which one fetus was stillborn and had apparently died before the onset of labor. Furthermore, only cases were selected in which the beginning of the last menstrual period was categorically stated.

Since our prime purpose in this portion of the study was to compare the average duration of twin pregnancy to the average duration of single pregnancy, we studied 1,290 single gestations excluding cases in which the onset of labor was hastened by some pathologic state or artificial means. The cases were also chosen so that the single pregnancy series was identical to the twin pregnancy group in respect to the proportion of multiparas, primiparas, colored and white. From Fig. 1 it appears that a twin pregnancy usually terminates more than

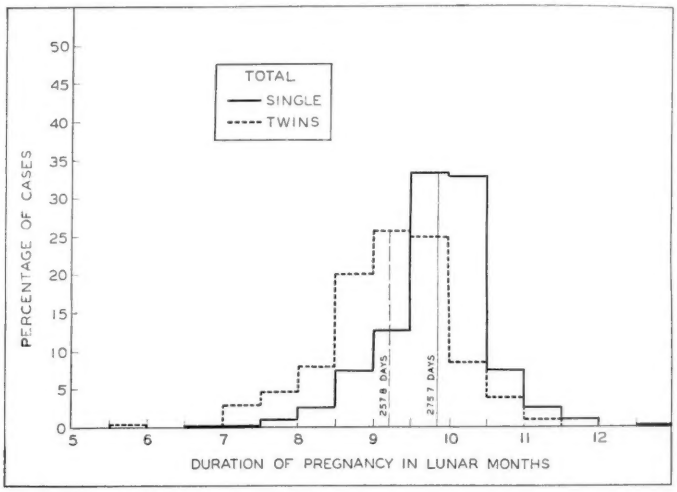

Fig. 1.—Duration in lunar months of viable twin pregnancies compared with single pregnancies occurring in the same clinic population. The mean duration is given in days for each group. The statistical material for both Fig. 1 and Table II was arranged and analyzed by the Statistical Department of The Johns Hopkins Hospital under the direction of Dr. E. L. Crosby.

two and one-half weeks before the ordinary single pregnancy: 257.8 days vs. 275.7 days, counting from the first day of the last menstrual period. It is to be noted that the average length of single pregnancy is four to seven days shorter than usually stated, but it must be borne in mind that our method of computation includes all gestations leading to viable infants, not solely "term" infants, and therefore contains many pregnancies resulting in premature infants. In the usual computations of length of pregnancy, all gestations resulting in infants weighing less than 2,500 or, in some even 3,000 grams, are excluded.

It is interesting that Colloridi[3] of Milan found the average length of pregnancy in his 359 twin cases precisely the same as ours, 258 days. In McClure's[4] study of 164 Irish twin pregnancies, 45 per cent terminated more than twenty-one days before the expected date of confinement and 64 per cent more than fourteen days.

Two other facts about the duration of pregnancy are revealed from a study of Table II. In the first place in both single and twin pregnancies parity played little role. In the single pregnancy group the primiparous woman had only 0.8 of a day shorter gestation than the multiparous woman. In twin gestations her pregnancy was briefer by two days. A second fact of interest revealed by Table II is that in both single and twin gestations the colored woman had a significantly shorter pregnancy than the white. In single pregnancies this difference amounted to 5.2 days and in twin pregnancies to 3.5 days. It is difficult to explain this fact since syphilitic patients were excluded from both series.

TABLE II

	SINGLE			TWINS			
	NO. OF CASES	MEAN LENGTH OF PREGNANCY IN DAYS	STANDARD DEVIATION	NO. OF CASES	MEAN LENGTH OF PREGNANCY IN DAYS	STANDARD DEVIATION	DIFFERENCE BETWEEN SINGLE AND TWIN PREGNANCIES IN DAYS
Grand total	1,290	275.7	18.7	247	257.8	22.5	17.9
White	621	278.4	18.1	121	259.6	20.6	18.8
Colored	669	273.2	18.9	126	256.1	24.1	17.1
Primiparous	321	275.1	18.5	6	256.3	19.8	18.8
Multiparous	969	275.9	18.8	186	258.3	23.3	17.6
White primiparous	150	277.8	20.1	29	255.1	19.4	22.7
Colored primiparous	171	272.7	16.5	32	257.3	20.0	15.4
White multiparous	471	278.6	17.4	92	261.0	20.8	17.6
Colored multiparous	498	273.4	19.6	94	255.7	25.3	17.7

WEIGHT GAIN

Unfortunately, the lack of reliable data in regard to the patient's nonpregnant weight precluded an analysis of the weight gain during twin pregnancy. However, in 106 of the more recent hospital cases the history contained the patient's weight at the onset of labor and her weight on discharge from the hospital ten to fourteen days post partum. The average difference between the two was 13.00 kg. (28.70 pounds). This can be compared to Dr. Stander's[5] experience at the New York Lying-in Hospital where he found an average difference of 7.85 kg. (16.89 pounds) between the admission and discharge weights in 400 unselected cases, all but a few of which must have perforce been single pregnancies. Our twin series showed a 71 per cent greater weight loss which presumably means that the woman with twins gains about 70 per cent more than the woman with a single fetus.

We divided the 106 cases into various groups. The 35 primiparas showed an average weight loss of 11.11 kg. (26.75 pounds) and the 19 para v or greater, 14.57 kg. (32.16 pounds). Forty-two women with hypertensive toxemia showed an average post-partum weight loss of 14.77 kg. (32.59 pounds) in contrast to an average weight loss of 11.89 kg. (26.15 pounds) in 64 normal patients. Twenty-four single-ovum twin pregnancies had an average weight loss of 12.15 kg. (27.04 pounds) and 73 double-ovum pregnancies 13.38 kg. (29.54 pounds). The slight difference between the two is probably on account of the higher proportion of multiparas in the double-ovum group.

Table III demonstrates: first, that in twin pregnancy the magnitude of the post-partum weight loss varies directly with the combined weight of the two fetuses, and, second, that the combined weight of the two fetuses is related to the parity of the patient. The latter point will be developed in greater detail in a subsequent paper on the newborn.

TABLE III

COMBINED FETAL WEIGHTS	NUMBER OF CASES	AVERAGE WEIGHT LOSS IN POUNDS	AVERAGE PARITY (NOT INCLUDING PRESENT TWIN PREGNANCY)
6,500-7,500	7	39.3	5.3
5,500-6,500	23	32.8	2.8
4,500-5,500	43	28.0	2.4
3,500-4,500	22	24.4	1.2
Under 3,500	10	22.3	0.8
Total	106		

COMPLICATIONS OF PREGNANCY

Hydramnios.—The study of this complication is most unsatisfactory because of the inexact criteria upon which the diagnosis is made. One observer will call an amount of amniotic fluid excessive which another will call normal, and vice versa.

Yet it is generally agreed that hydramnios is several times as frequent in twin as in single pregnancy. The only disagreement rests in the magnitude of its occurrence. Hinselman states that hydramnios is found in 0.5 to 1.0 per cent of single pregnancies. The reported incidence for twins varies from 3.6 per cent (McClure) to 24 per cent (McIlroy). Rieder found it in 8 per cent as did Szendi[6] in his series from Hungary. Gernez and Omez[11] noted it in 7.6 per cent of their 236 twin pregnancies from Lille; in three it was so marked that abortion had to be induced by rupture of the membranes. It is unlikely that the true incidence varies as much as the diagnostic criteria. Hydramnios was diagnosed in 40 of our 573 twin pregnancies, an incidence of 7 per cent. It was noted 21 times in 281 term pregnancies (7.5 per cent), 13 times in 222 premature pregnancies (5.9 per cent), and 6 times in 70 abortions (8.6 per cent). Most investigators have observed it to be more frequent in single ovum twinning. Gaehtgens[7] reports 45 cases of acute hydramnios from Kiel, 11 of which occurred

in twins, 7 being monozygotic. However, of the 31 cases of hydramnios at the Hopkins in which the relations of the membranes was definitely determined, 7 (22.6 per cent) were single ovum and 24 (78.4 per cent) double ovum; approximately the proportion of single to double-ovum pregnancies in the whole series. Of the 40 patients in whom hydramnios was diagnosed, 82.5 per cent were multiparas, slightly higher than the proportion of multiparas in the whole series (77.4 per cent). It is interesting that the maximum amount of fluid occurred in two abortions, 7 and 5.9 liters. Seven of the 40 cases were associated with toxemia (17.5 per cent).

MISCELLANEOUS COMPLICATIONS

There were 12 cases of heart disease, 6 of tuberculosis, 3 of epilepsy and 52 of syphilis. These occurred with the same frequency as in single births. The 7 cases of ante-partum bleeding, 4 premature separation of the placenta and 3 placenta previa, will be discussed in the succeeding paper on labor.

Pyelitis.—Beginning with 1926 the incidence of ante-partum pyelitis could be accurately determined on the Obstetrical Service of the Johns Hopkins Hospital, for at this time the unit system of histories was inaugurated. This meant that separate admissions for the same patient were indexed under one number and placed in the same folder to form a single book, and thus it would be obvious to an investigator, if the patient were hospitalized for pyelitis at any time during the course of pregnancy or late in the puerperium. Much to our surprise there was only one case of ante-partum pyelitis in the 164 registered patients who bore twins since that date, an incidence of 0.61 per cent. Two other registered patients developed pyelitis in the puerperium. In addition, there was one post-partum case in 42 unregistered patients, the three giving a total incidence of 1.45 per cent in the 206 puerperal women who had delivered twins. In view of the supposed connection between pressure from the pregnant uterus with the etiology of this complication, it is truly remarkable that only one case of ante-partum pyelitis occurred in 164 twin pregnancies, for certainly the pressure from a uterus containing twins is greater than that from a uterus containing but one child. Furthermore, the low incidence of pyelitis in the puerperium was not anticipated.

Anemia.—The development of anemia during pregnancy is in large part the result of iron depletion through the fetal trophoblast. It is reasonable to suppose that a twin pregnancy with its additional fetal demands and its greater placental area would deplete the mother's hemoglobin, even more than a single pregnancy. In order to test this hypothesis, we compared the hemoglobin readings in 1,962 single pregnancies with 47 patients with twins. The readings in both groups were made by the same technician upon the same Sahli instrument, which was checked every three months against the Van Slyke chemical method of direct hemoglobin determination. The hemoglobin was taken before any iron therapy had been given, that is, at the patient's first visit, which was any time between the twelfth and fortieth weeks.

In 11 per cent of the white patients with single pregnancies, the hemoglobin was below 70 per cent in contrast to 40 per cent of the 15 with twins. In the colored, the difference between the two series was just as striking, for only 30 per cent of the single pregnancies had a hemoglobin below 70 per cent, while 72 per cent of 27 twin pregnancies had figures this low. It is worthy of mention that 20 per cent of the white patients with twins and 35 per cent of the colored had hemoglobins of 60 per cent or less before iron therapy was begun.

Toxemia.—On the basis of theories advanced to explain toxic vomiting, one would expect to find it more frequently during twin gestations. If it is caused by hormonal products of the placenta, these should be increased by the greater amount of secreting trophoblast, and if due to metabolites from the fetus, these should be doubled by two embryos. On this basis we approached this phase of the study with an erroneous prejudice; the data completely contradicted our hypothesis. For at the Hopkins a second fetus has never been recognized in cases of toxic vomiting for which therapeutic abortion had to be done. Furthermore, not a single one of the 573 twin pregnancies had to be interrupted for vomiting, and only two of the 205 mothers with twins for whom there were unit histories, had to be hospitalized during pregnancy because of vomiting. Both of these patients were successfully treated and discharged from the hospital to go on to term, although one was ill enough to require three separate hospital admissions.

We also analyzed the histories of 204 patients with twins to compare their ordinary nausea and vomiting with patients carrying single pregnancies. As shown in Table IV the patients with twins were divided into several classes, the classes ranging from the complete absence of these symptoms to their presence in a marked degree. In summary, two-fifths of the patients had no nausea or vomiting, two-fifths were mildly affected, and one-fifth severely. This proportion differs but little, if at all, from the ordinary situation in single pregnancies. Colloridi[3] found ptyalism, nausea, or vomiting in 76 per cent of his twin pregnancies, which he considered slightly more frequent than in single pregnancies. Our findings and those of Colloridi should be checked by other investigators, and if corroborated they may call for critical consideration of the current theories of vomiting.

TABLE IV

DEGREE	NUMBER	PER CENT
No nausea or vomiting	84	41.2
Nausea but no vomiting	6	3.0
Mild nausea and vomiting	65	31.8
Moderately severe nausea and vomiting	38	18.6
Very severe nausea and vomiting	11	5.4
Total	204	100.0

Hypertensive States.—The standard criterion used in the Johns Hopkins Obstetrical Department for the diagnosis of hypertensive toxemia

has been adopted in this study, that is, a rise in blood pressure to 140/90 at any time during pregnancy or the puerperium. Judged by this, from 1896 to 1937, there were 106 cases of hypertensive toxemia in 499 pregnancies with viable twins,* an incidence of 21.3 per cent. On closer scrutiny it is seen that the occurrence of toxemia was frequent in our recent cases of twins and relatively rare in the earlier ones. In 281 cases before Jan. 1, 1926, there were 31 instances of toxemia (11 per cent) and in 218 cases since, 77 (35.32 per cent). It is obvious that the disease has not become more than three times as common but that with modern diagnostic methods it is more frequently recognized. No routine blood pressures were taken on the Johns Hopkins Obstetrical Service in the first two decades of this study. In eclampsia and very severe pre-eclampsia only, they were recorded with the Riva-Rocci sphygmomanometer. We shall therefore exclude all cases before Jan. 1, 1926, and submit to closer scrutiny the 218 cases of viable twins occurring thereafter.

The 35 per cent incidence of hypertensive toxemia in our recent viable twin pregnancies is difficult to compare with other investigators, since they do not list their criteria for the diagnosis of toxemia. Dame McIlroy[2] states that 46 per cent of her cases had one of the various forms of toxemia, "albuminuria, dimness of vision, raised blood pressure, etc." McClure[4] had a total pre-eclamptic and eclamptic rate of 40 per cent in 165 cases.

The frequency of hypertensive toxemia in viable twin pregnancies is two and one-half times greater than that found by Dr. C. H. Peckham in the total viable births at the Johns Hopkins during approximately the same period. In them he noted a total incidence of toxemia of 14.71 per cent. If the twin pregnancies with toxemia are separated into eclamptics, pre-eclamptics, and other hypertensives (the latter made up of low reserve kidney, nephritic and unclassified cases), we can compare their incidence directly with Peckham's figures.

TABLE V. INCIDENCE OF LATE PREGNANCY TOXEMIA SINCE 1926

	IN ALL VIABLE PREGNANCIES	IN VIABLE TWIN PREGNANCIES
Eclampsia	0.70%	3.21%—4½ times
Pre-eclampsia	0.75%	2.29%—3 times
Low reserve kidney, Nephritis, Unclassified	13.26%	29.82%—2 times
Total	14.71%	35.32%—2½ times

Of 77 toxemic patients with twins 59 (76.6 per cent) were multiparas and 18 (23.4 per cent) primiparas. The parity proportion for 141 normal patients in the same group was 109 (77.3 per cent) multiparas and 32 (22.7 per cent) primiparas. These figures suggest that parity plays little or no role in the occurrence of toxemia in twin pregnancy.

*Six cases of toxemia resulting in dead fetuses, each weighing less than 1,500 gm., were added to 493 viable pregnancies. In the general statistics these six cases have been considered abortions.

On dividing 77 toxemic pregnancies into single and double ovum, we find that 79.2 per cent were double ovum and 20.8 per cent single ovum. The relation of the membranes in the normal pregnancies was double ovum 77.3 per cent and single ovum 22.7 per cent. It is hazardous to draw any conclusions from such a small series (77 cases and 141) but at least it suggests that monozygotic and dizygotic twinning predispose equally to pregnancy toxemia.

Forty-four (57.2 per cent) of 77 toxemic twin patients were delivered of a fetus weighing more than 2,500 gm. and 33 (42.8 per cent) with both fetuses weighing less. Of 141 normal patients, 79 (56.0 per cent) were delivered of term-sized fetuses and 63 (44 per cent) of premature infants. The close approximation of these figures in the toxemic and nontoxemic groups implies that toxemia does not tend to produce premature labor in twin gestations. Furthermore the size of the fetal mass seems to exert little or no influence on the occurrence of the condition.

Since the dramatic convulsions of eclampsia were just as easily recognized in the "nineties" as now, it seemed justifiable to include all the eclampsia which has occurred since the inception of our obstetric service in the study of this disease in twin pregnancy. There were 17 eclamptic patients in 499 viable twin pregnancies, an incidence of 3.41 per cent; 10 of these occurred in the first 281 cases (3.56 per cent), and 7 in the last 218 (3.21 per cent).

Since there is unanimous agreement in regard to the diagnosis of eclampsia, its frequency in the twin pregnancies of other clinics can be compared accurately to our own. McIlroy[2] found it in 5.88 per cent, Colloridi[3] in 1.9 per cent, McClure[4] in 2.4 per cent, and Gernez and Omez[11] in 2.33 per cent. Adding the cases from these authors to our own, we find 36 cases of eclampsia in a total of 1,288 twin pregnancies (2.79 per cent). The frequent association of twinning and eclampsia can be approached from another point of view, the percentage of twins in the total births compared to their percentage among all eclamptic cases. According to the current edition of *Midwifery by Ten Teachers*[8] twin births occur in 1.2 per cent of all births, while they made up to 4.7 per cent of a series of 1,524 eclamptic patients.

Stroganoff and Davidovitch[9] in a recent article on 200 eclamptic patients treated with magnesium sulfate reported that of 10 with twins 4 died; indeed from these 10 came two-thirds of his total maternal deaths. From this, one might suppose that when eclampsia complicates twin pregnancy it occurs in an especially malignant form. To learn if this were true we studied our 17 cases of eclampsia with great care, comparing them with the eclamptic women with single pregnancies. There was no essential difference between the two in regard to maternal mortality. Three of the 17 eclamptic patients with twins died (17.6 per cent) and 60 of the 370 single pregnancies (16.3 per cent). The proportion of mild to severe and ante partum to post partum was relatively the same in each. One significant difference was the proportion of multiparas to primiparas. In eclamptic patients with twins

58.8 per cent were multiparas, while in eclamptic patients with single pregnancies only 33.9 per cent were multiparas. The higher incidence of multiparas in the twin group is partially explained by twinning being more common in multiparas. In 544 patients with twins, 77.4 per cent were multiparas, while in 29,227 total births at the Johns Hopkins 64.2 per cent were multiparas.

Maternal Mortality and Its Association With Toxemia.—Despite the fact that in this paper we do not intend to analyze the problem of maternal mortality in multiple pregnancy, we think it germane to point out its association with toxemia. In a total of 1,163 cases of viable twin pregnancy, 660 collected from the recent literature (McIlroy,[2] McClure,[4] Gidalewitsch,[10]) to which our 503 cases were added, there were 23 maternal deaths (2 per cent). In 11 the primary cause of death was toxemia; 8 eclampsia, 2 chronic nephritis, and one pre-eclampsia which developed into acute yellow atrophy. In 3 other fatal cases the toxemia played an important contributory role: in two it complicated postdelivery shock and in one heart disease. Thus toxemia was either the primary or secondary factor in 61 per cent of the maternal twin deaths. Toxemia was either a primary or secondary cause in the seven maternal deaths of our own series.

SUMMARY

1. The diagnosis of twins appears to present difficulties, for it was missed in almost one-third of our cases during the past twelve years. When both infants weighed less than 2,500 gm., one-half of the twin pregnancies remained undiagnosed and when the larger twin weighed 2,500 gm. or more, the correct ante-partum diagnosis was made in slightly more than 70 per cent.

2. With classification of term, premature, or abortion on the sole basis of the weight of the larger fetus, one-half of the twin pregnancies ended in term labors, three-eighths in premature births and one-eighth in abortions. Of viable twin pregnancies 56 per cent terminated in term-sized fetuses and 44 per cent in premature infants, in contrast to 91 per cent and 9 per cent of single pregnancies. The tendency to premature twins was more marked in primiparas.

3. Viable twin pregnancies terminate eighteen days earlier than single pregnancies. The duration of pregnancy was not affected by parity, but it was influenced by race, the colored patients having shorter twin and single pregnancies.

4. Women with twins gain 70 per cent more than women with single pregnancies. The gain is greater in those with toxemia. Furthermore the amount gained increases with advancing parity, which is due to the larger size of the twin fetuses born to grande multiparae.

5. The exact frequency of hydramnios was difficult to determine because of failure to measure the amniotic fluid in most cases. The condition was diagnosed by palpation in 7 per cent.

6. Twin pregnancy does not increase the frequency of ante-partum or post-partum pyelitis.

7. Physiologic, secondary anemia is more frequent and more profound in patients with twin pregnancy.

8. Contrary to general experience we found that toxemic and functional vomiting were no more common in twin than in single pregnancy.

9. Hypertensive toxemia is two and one-half times as frequent in twin pregnancy. Neither parity, zygosity, nor the combined fetal weights appears to affect this frequency.

10. Eclampsia and pre-eclampsia are increased more than other varieties of hypertensive toxemia, the former occurring once in every 30 twin pregnancies.

11. The gravity of the association of toxemia with twin pregnancy is attested by the fact that 61 per cent of maternal twin deaths were associated with toxemia.

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RUPTURED GRAAFIAN FOLLICLE AND CORPUS LUTEUM WITH INTRA-ABDOMINAL HEMORRHAGE SIMULATING ACUTE APPENDICITIS AND RUPTURED ECTOPIC PREGNANCY

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Israel[1] in a recent survey of this interesting subject reports that up to the present time more than 300 case reports of ruptured Graafian follicle and corpus luteum with intra-abdominal hemorrhage simulating acute appendicitis and ruptured ectopic pregnancy have appeared in the literature. Doubtlessly there have occurred others, for many patients with rupture of a Graafian follicle or corpus luteum with mild hemorrhage do not consult a physician. Also many patients with slight hemorrhage, treated surgically, are never correctly diagnosed.

As stated by Johnson,[2] Meigs and Hoyt,[3] Pratt,[4] Sackett,[5] Miller,[6] and Israel,[7] ruptured Graafian follicle and corpus luteum with mild bleeding is most often confused with appendicitis, whereas rupture with copious intra-abdominal hemorrhage simulates ruptured ectopic gestation. Graafian follicle rupture with mild bleeding is usually sudden in onset, with moderate to severe pain over the involved adnexa. This

condition occurs most frequently in females between 16 and 30 and very infrequently before the onset of menstruation or immediately before the menopause.[3, 5, 7] Nausea and vomiting occur but are not predominating symptoms of rupture of the ovary with hemorrhage. Leucocytosis and fever are found in both conditions. They are dependent, in rupture of the ovarian sexual apparatus, upon the reaction of the peritoneum to the foreign substance, i.e., follicular fluid or blood.

Rupture of the Graafian follicle usually occurs during the first three weeks of the menstrual cycle and most often between the twelfth and eighteenth days, whereas corpus luteum rupture occurs most frequently within the last week of the cycle or during the menses.[3, 4, 7] The history, therefore, is essential and the menstrual cycle should be carefully investigated. Patients sometimes give a history of onset associated with trauma, i.e., walking, strenuous exercise,[8] or a blow to the lower abdomen.[9] Many cases reported in the literature trace their onset to the sexual act.[2, 10-12] In the cases herein reported trauma was apparently not a predisposing factor.

On examination, if seen immediately after the accident, and if bleeding has been profuse, the patient may show signs of mild shock characterized by pallor, rapid pulse, and low blood pressure. Without a complete investigation one could easily confuse these findings with those frequently seen in ruptured ectopic pregnancy. If rupture is associated with slight hemorrhage, and if the right ovary is involved, the condition is usually confused with appendicitis. Examination of the abdomen will reveal palpable right rectus spasm, direct and rebound tenderness, however, with maximum tenderness somewhat below McBurney's point. Examination per vaginam because of the pain associated with manipulation of the internal genitalia causes one to suspect pelvic disease rather than appendicitis. In some instances slight enlargement of the ovary, or the presence of a definitely palpable mass, which is tender on manipulation, will focus one's attention on the internal genitalia rather than the appendix.

In mild hemorrhage there is no bulging of the cul-de-sac of Douglas such as is frequently encountered in ruptured ectopic pregnancy. The latter can be differentiated on the basis of missed periods, bleeding, early signs of pregnancy, and the appearance of a tender tubal mass. Where hemorrhage is fulminative it is not so important to differentiate as the exact cause preoperatively, for in any event operation is imperative.

The importance of a correct diagnosis is apparent when we realize that the patient, in whom rupture with mild hemorrhage occurs, is not necessarily a candidate for surgery whereas acute appendicitis or ectopic pregnancy is definitely a surgical problem. Brakely and Farr,[13] and Pratt,[4] state that in the mild cases, with rare exceptions, operative treatment is contraindicated. However, if the symptoms and signs do not subside and the correct diagnosis is still in doubt, operation is the procedure of choice. This decision is based on the premise of the grave danger associated with delay in acute appendicitis, and the minimal risk of an exploratory procedure. As stated by Meigs and Hoyt,[3] it is difficult to treat conservatively a patient who *might have* early acute appendicitis. In any event, if operation is decided upon the incision should be so placed as to give adequate visual exposure to the internal genitalia. There are doubtlessly some normal

appendices removed through a McBurney incision when the true lesion, if exposure were adequate, would have been found in the pelvis.

Upon operation one finds many gradations of bleedings, from 10 c.c. of blood-tinged, straw-colored fluid to profuse intra-abdominal hemorrhage of a liter or more of blood. Occasionally the actively bleeding vessel may be seen, as was the case in one instance only of the series herein reported, but most often there is only a generalized oozing coming from the rupture site. Where the laceration is not extensive, removal of the clot with lock stitch closure of the defect, using fine catgut suture material, will control the hemorrhage. However, it may be necessary to remove the entire adnexa to control the bleeding. Additional indicated surgery such as appendectomy, cysto-oophorectomy, or suspension of the uterus, is permissible, depending on the patient's general condition.[1]

During the five-year period between 1932 and 1937, 35 cases of Graafian follicle or corpus luteum rupture have been collected from the surgical records of the City Hospital of Akron. The frequency with which this condition has been confused with acute appendicitis will be seen from Table I. Of these 35 patients, 30 were operated upon; none of which was correctly diagnosed preoperatively. Five patients with a clinical diagnosis of ruptured Graafian follicle were observed during 1936 and 1937 in the hospital, recovered, and were discharged without operation. One patient whose case history is abstracted below, had a ruptured right corpora lutea with active hemorrhage, intact left corpora lutea, and also incomplete intrauterine abortion. Of the 30 operated upon the preoperative diagnosis was appendicitis in 24 and ectopic pregnancy in six. Ruptured Graafian follicle occurred 18 times and ruptured corpus luteum 12 times. At the time of operation the offending ovary was found 20 times on the right and five times on the left side.

TABLE I. PREOPERATIVE DIAGNOSIS

APPENDICITIS		ECTOPIC PREGNANCY	
Acute	13	Right	2
Subacute	10	Left	4
Chronic	1		

The one outstanding symptom complained of with a marked degree of regularity was sudden pain; this occurred 30 times. In every instance it was located low down on either the right or the left side, and infrequently associated with nausea or vomiting. Weakness was recorded 12 times, and fainting twice. The pain which at first was said to be localized would later become diffuse and was intensified by motion, i.e., walking, bending, or stretching. In 24 instances the pain started on the right side. This probably accounts for the 24 preoperative diagnoses of appendicitis.

From the charts reviewed the physical examinations revealed various degrees of direct and rebound tenderness in one or the other lower quadrants. This tenderness was usually below McBurney's point.

The temperature varied from subnormal to a maximum of 101.2° F. The pulse varied from normal to 130/minute. Pelvic examination was recorded 15 times, rectal examination three times, and in 17 instances there was no record of either pelvic or rectal examination. Of the 15 pelvic examinations recorded, six patients were reported to have had bilateral adnexal tenderness and no masses. Eight had right adnexal tenderness associated with an enlarged right ovary. One patient had an enlarged and tender left ovary. The three rectal examinations recorded and which were done on unmarried girls revealed right adnexal tenderness only.

Among the patients operated upon there were 25 nulliparas and 5 multiparas whose ages ranged from 14 to 32 years. Twenty-six of these women were between 14 and 22 and the remaining 6 between 22 and 32 years of age. Ruptured Graafian follicle with intra-abdominal hemorrhage occurred only once in the multiparous group.

Since there is normally a certain degree of regularity associated with follicle formation, ovulation, and corpus luteum appearance, one would expect to be able to correlate rupture of the Graafian follicle or corpus luteum and hemorrhage with the menstrual cycle. Table II gives this relationship.

TABLE II

MENSTRUAL DAY	RUPTURED GRAAFIAN FOLLICLE	RUPTURED CORPUS LUTEUM
1-14	14 Cases	None
14-21	2 Cases	1 Case
21-31	None	7 Cases
Intramenstruum	None	1 Case
Not stated	2 Cases	3 Cases

Of the 18 cases of Graafian follicle rupture with hemorrhage, 14 occurred between the twelfth and eighteenth days, one on the tenth day, and one on the twenty-first day. In the remaining three cases there was no record of the menstrual day on which rupture occurred. Nine of the 12 cases of corpus luteum rupture of which we have information concerning the menstrual day, occurred between the twenty-first and thirty-first days. This is in keeping with the previously reported cases found in the recent literature.[2, 4-6] One patient was menstruating when admitted; however, this case was complicated by an undiagnosed incomplete abortion. From our material one must assume that corpus luteum rupture occurs during the last week of the menstrual cycle, whereas Graafian follicle rupture occurs most often during the intermenstruum.

The degree of hemorrhage found at operation in the two conditions is outlined in Table III.

TABLE III

	SLIGHT, LESS THAN 30 C.C.	MODERATE, LESS THAN 100 C.C.	PROFUSE, LESS THAN 500 C.C.	NOT STATED
Graafian follicle	9 Cases	None	4 Cases	5 Cases
Corpus luteum	None	5 Cases	7 Cases	

Here we see that 9 cases of Graafian follicle rupture were associated with mild hemorrhage. The five patients with Graafian follicle rupture where the degree of hemorrhage was not recorded in the operative descriptions were operated upon through a McBurney incision. I assume that we should classify these in the category of slight hemorrhage. This would bring the group associated with less than 30 c.c. of blood loss up to 14. There were four cases of rupture of Graafian follicle with profuse hemorrhage; in each instance the entire involved ovary was removed. Of the 12 ruptured corpora lutea with hemorrhage, 5 were associated with moderate and 7 with profuse hemorrhage.

The McBurney incision was used 18 times, right rectus 6, and the midline 6 times. Nine ovaries, 4 tubes, and 30 appendices were removed. Of the 21 ovaries allowed to remain in situ, after recognition of the site of rupture, only 12 necessitated suturing to control the hemorrhage. In the remaining 9 involved ovaries bleeding had become quiescent and suturing was unnecessary. In no instance was a diagnosis of acute appendicitis made from the microscopic sections of the appendices removed.

ABSTRACTS OF CASE HISTORIES

CASE 1.—Mrs. C. H., a white female, aged 31 years, para ii, entered the hospital on Oct. 1, 1937 with a history of having missed her menstrual period in August. However, on September 14, she began having severe menstrual-like cramps, followed by slight vaginal bleeding. Three hours after the onset of pain and bleeding she began to hemorrhage and passed clots and some pieces of "flesh" which she identified as fetal membranes. Ever since this episode she has had dark brown vaginal discharge and irregular vaginal bleeding. Two days prior to her admission she had a sudden pain in the left lower quadrant which made her very weak; however, she did not faint. Following her attack of sudden pain there followed persistent soreness throughout her lower abdomen.

On physical examination the patient did not appear acutely ill. The abdomen was scaphoid, there was definite direct and rebound tenderness in the left lower quadrant. No mass could be palpated. Colostrum could be expressed from the breasts. Pelvic examination revealed some blackish vaginal discharge, and a patulous, multiparous cervix which felt soft. The uterus was slightly enlarged and soft. Motion of the cervix caused pain in the left adnexal region. The latter presented a small tender mass. There was no bulging of the cul-de-sac of Douglas. The laboratory findings revealed a white blood count of 7,100, 82 per cent neutrophiles, red blood count 3.8 million and hemoglobin 12 gm., 78 per cent. The urine was negative. The preoperative diagnosis was left ruptured ectopic tubal pregnancy. A dilatation and curettage revealed a moderate amount of tissue grossly identified as decidual tissue. A midline abdominal incision was made and a moderate amount of free and clotted blood was found in the cul-de-sac of Douglas. The left ovary showed a large recently ruptured corpus luteum which contained a firm clot and was not actively bleeding. The right ovary contained a normal appearing unruptured corpus luteum. A left salpingo-oophorectomy and appendectomy was done. The pathologist reported that the appendix measured 9½ by ¾ cm., and appeared grossly normal. The ovary showed a large hemorrhagic corpus luteum with diffuse hemorrhage. Endometrial curettings showed chorionic villi. The tube and appendix were microscopically normal. The final diagnosis was: (1) incomplete abortion, (2) ruptured left corpus luteum with hemorrhage, (3) intact right corpus luteum.

CASE 2.—L. F., aged 25, single, office worker, was admitted to the hospital Aug. 5, 1937 with a diagnosis of possible acute appendicitis. She had always been in excellent health; however, twenty-four hours prior to admission, while riding in an

auto, she was suddenly taken with sharp knifelike pains in right lower quadrant. She went directly home and obtained partial relief by lying in bed. She experienced some nausea but no vomiting. There had been no constipation. The pain which was in the right lower quadrant changed to a dull ache, spreading over the entire lower abdomen and was made worse on motion. The next day the patient went to work but she did not feel right. She was advised to enter the hospital. The last normal menstrual period occurred July 22, 1937 and was uneventful.

Physical examination was negative except for tenderness in the right lower quadrant below McBurney's point. There was slight right rectus spasm. Pelvic examination was negative except for a tender right ovary. On August 6, the white blood count was 9,000 with 57 per cent neutrophiles and the urine was negative. On August 7, the white blood count was 9,800 with 74 per cent neutrophiles. On August 8, the white blood count was 6,200 with 70 per cent neutrophiles. The patient remained in the hospital under observation for three days during which time she recovered completely and was discharged with a diagnosis of ruptured right Graafian follicle with slight hemorrhage.

CASE 3.—E. R., a single girl, aged 19 years, was admitted as an emergency case Jan. 22, 1936, because of right lower quadrant pain which came on suddenly about twenty-four hours previously. The patient stated that the pain was sudden and knife-like, causing her to sit down. Later she became weak but did not faint. Gradually the pain became dull and spread over the entire abdomen. She had vomited four times in the past twenty-four hours. The last normal menstrual period occurred Jan. 12, 1936.

Physical examination was negative except for direct and rebound tenderness over the lower abdomen, slightly worse over the right side. All the abdominal tenderness seemed centered in the pelvis. Pelvic examination was negative except for right adnexal tenderness. The right ovary seemed larger than normal. The white blood count was 15,300 with 77 per cent neutrophiles. The urine was negative. The patient was given an enema which did not relieve her condition. The diagnosis on admission lay between possible acute appendicitis, possible acute salpingitis and possible ruptured right Graafian follicle with mild hemorrhage. The patient remained in the hospital five days during which time she gradually (third day) recovered, with a gradual recession of the leucocyte count from 13,200 on January 23 down to 6,000 on January 26. The final diagnosis was ruptured right Graafian follicle with mild hemorrhage.

CASE 4.—M. L., aged 15 years, while in the process of getting out of bed Jan. 15, 1937 was taken suddenly with right lower quadrant pain which made her cry out and double up. She became weak and nauseated but did not vomit. The pain gradually became dull, and spread over the lower abdomen. Since the patient had been previously told she had a bad appendix she was immediately taken to the hospital. On admission she stated that she had had in the past year several similar attacks of lower abdominal pain but never so severe. Her last normal menstrual period was Dec. 30, 1936 and was uneventful. There had been no constipation.

The physical examination was negative except for some muscle spasm over both right and left lower quadrants. There was direct and rebound tenderness in the right lower quadrant below McBurney's point. No masses were palpated. Rectal examination revealed pain referred to the right side on motion of the cervix. The right adnexa were larger than the left and definitely tender. The white blood count was 10,000 with 68 per cent neutrophiles. Temperature was 99.2° F. and the pulse was 90. The patient remained in the hospital for three days during which time the symptoms completely disappeared. The white blood count was 6,000 with 52 per cent neutrophiles on the day of discharge. The final diagnosis was ruptured right Graafian follicle with slight hemorrhage.

CASE 5.—L. Mc., aged 22 years, a nullipara, entered the hospital as an emergency on March 7, 1936 because of a history of sudden knife-like lower abdominal pain

coming on during coitus. The patient said she became weak, nauseated, and vomited once. These symptoms came on about ten minutes after the pain. Her last normal menstrual period was Feb. 26, 1936 and was uneventful.

The physical examination was negative except for tenderness in the right lower quadrant. Pelvic examination revealed normal internal genitalia except for the right adnexa which were very tender on palpation. They did not seem enlarged. Motion of the cervix caused right sided pain. The white blood count was 11,800 with 89 per cent neutrophiles. The urine was negative, and the temperature and pulse rate were normal. The tentative diagnosis was ruptured right Graafian follicle with slight hemorrhage. The patient remained in the hospital for three days during which time she recovered completely. The white blood count on the third day returned to normal.

CASE 6.—J. L., aged 17 years, unmarried, had her last normal menstrual period on Sept. 16, 1936. While at work in the hospital on Sept. 29, 1936 as an undergraduate nurse, she was suddenly taken with a sharp right lower quadrant pain which caused her to double up. She stated that for the next half hour she became very weak and nervous. The pain was sharp at first, changed to a dull ache throughout the lower abdomen, and was worse when she walked. She had never experienced anything like this before.

Physical examination was essentially negative except for some deep palpable tenderness in the right lower quadrant below McBurney's point. Rectal examination revealed pain on motion of the cervix and a tender right adnexa which did not appear enlarged. The left adnexa were neither tender nor enlarged. The white blood count was 12,800 with 84 per cent neutrophiles. The urine was negative, and the temperature was 99° F. The dull pain continued until 7:00 A.M., September 30, after which time it gradually subsided. The white blood count September 30 was 8,000 with 70 per cent neutrophiles. October 1, the white blood count was 6,200 with 62 per cent neutrophiles. The patient was discharged with a presumptive diagnosis of ruptured right Graafian follicle with slight hemorrhage.

SUMMARY AND CONCLUSION

1. Thirty cases of Graafian follicle and corpus luteum rupture with hemorrhage, operated upon with a tentative diagnosis of appendicitis or ruptured ectopic pregnancy, are reported.

2. Five additional cases are discussed. These patients were observed in the hospital for a maximum period of five days, and a clinical diagnosis of ruptured Graafian follicle with slight bleeding was made. All recovered without the aid of surgery.

3. The differential diagnosis between rupture of Graafian follicle and corpus luteum with hemorrhage and appendicitis or ectopic pregnancy is discussed.

4. The only characteristic symptom noted in rupture of Graafian follicle and corpus luteum was sudden pain and this occurred in every instance.

5. In this series rupture of the ovarian sexual apparatus occurred most frequently in young women up to 25 years of age and most often on the right side.

6. Correlation between ruptured Graafian follicle and corpus luteum with bleeding and the menstrual cycle is mentioned.

7. Similar quantities of blood loss were noted in both Graafian follicle and corpus luteum rupture.

8. It is suggested that when the diagnosis of lower abdominal conditions warranting surgery in the female is in doubt either right rectus

or midline incisions should be made, so that visual inspection of the internal genitalia may be accomplished.

9. Abstracts of five unoperated cases diagnosed ruptured Graafian follicle with slight intra-abdominal hemorrhage but not proved are presented. A case of ruptured left corpus luteum with hemorrhage complicated by incomplete intrauterine abortion is reported.

I wish to express my appreciation to Dr. Charles C. Pinkerton for many valuable suggestions in the preparation of this report and also to thank the Surgical Staff of the City Hospital of Akron for their permission to publish the cases herein reported.

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2108 First Central Tower

TUBAL STERILIZATION BY THE MADLENER TECHNIQUE*

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DURING recent years, the importance of contraception as well as sterilization for medical eugenic and social reasons in selected cases has gained widespread recognition.

Side by side with the endeavor of the numerous birth control clinics to find a reliable method of contraception, increasing attention has been given to the question of dependable permanent sterilization of women.

In men, sterilization is no longer a problem. Vasectomy is unanimously accepted as the procedure of choice because it fulfills, when properly performed, the requirements of ideal sterilization, including (1) absolute reliability, (2) minimum operative risk, (3) subsequently unimpaired health, and (4) undisturbed sex response.

In women, sterilization is still open to discussion. Female fertility has an amazing persistence. On one hand we may see it destroyed by an apparently insignificant infection. On the other hand we find it surmounting heavy odds. Conception has taken place after the removal of both tubes as in the cases reported by Lasch, Burkhard, Zangemeister, and once even following subtotal hysterectomy in a case reported by Liepman.

Considering this ability of the female organs to fulfill their biologic purpose, it is no wonder that surgical sterilization has met with difficulties. Nürnberger recorded in a comprehensive study of 305 sterilizations by various methods, 17, or 6 (5.7) per cent, failures.

*Read, by invitation, at a meeting of the Section on Obstetrics and Gynecology, New York Academy of Medicine, November 23, 1938.

Among the procedures mentioned by Nürnberger, the cornual wedge operation is comparatively the most reliable and still used a great deal. No pregnancy has occurred among the 64 cases of my own material (Table I), which has been followed up for more than two years.

TABLE I. SIXTY-FOUR STERILIZATIONS BY CORNUAL RESECTION

INDICATION	NUMBER OF CASES
Operations for prolapse (41 vesicovaginal interpositions)	43
Tuberculosis of lungs	12
Organic heart disease	4
Tracheostenosis	1
Voluntary sterilization	1
During cesarean operation	3
Total	64

Although the result is satisfactory concerning sterilization, these statistics are somewhat misleading, as many of the patients sterilized in the course of an operation for prolapse were of an age when conception, though possible, was less likely to occur.

Furthermore, the table does not indicate the frequent difficulty of controlling hemorrhage, especially in pregnancy, after the excision of a sufficiently deep cornual wedge.

The complete elimination of hemorrhage is one of the reasons for the increasing popularity of the "bloodless" tubal ligature advised by Madlener, which I have used as the procedure of choice since it has been published.

It is the purpose of this paper to give an account of the merits of the tubal sterilization devised by Madlener, because I feel that of all the procedures employed, this one is the most satisfactory.

The original technique consists of lifting up a generous loop of the Fallopian tube and crushing it with a clamp. The clamp is removed, and replaced by a ligature of nonabsorbable material.

In Table II, 147 sterilizations in my own experience are recorded. Most of them have been performed while I was connected with the Department of Gynecology at the State University of Iowa in Iowa City.*

In contradistinction to the cases of cornual wedge operation (Table I) these 147 sterilizations by the original Madlener method include only 58 patients with prolapse. The large majority were women of childbearing age, and in them the result was entirely favorable. The only failure occurred in a patient operated upon for prolapse.

Table III is a survey of all the cases reported in the literature up to September, 1938, as sterilized according to Madlener, including the author's 147 cases and the 157 sterilizations performed at the Gynecological Clinic of the Iowa University Hospital since July, 1934.

*I am indebted to Dr. E. D. Plass who has allowed me to present this material as well as the number of patients operated upon at the Department of Gynecology from July, 1934 to September, 1937, listed in Table III.

TABLE II. 147 STERILIZATIONS BY ORIGINAL MADLENER TECHNIQUE (PERSONAL CASES)

INDICATION			NUMBER OF CASES	
Operations for prolapse (38 vesicovaginal interpositions)			58	(1 failure)
Pulmonary tuberculosis (1 bronchiectasis, 1 lung abscess)			15	
Organic heart disease			12	
Pelvic pathology			5	
Spondylitis			1	
Kidney disease			6	
Eye diseases			3	
Mental and organic brain diseases	Feeble minded	10		
	Dem. precox	1		
	Psychosis	8		
	Mult. sclerosis	2	27	
	Encephalitis	1		
	Epilepsy	5		
Social			17	
Voluntary			3	
Total			147	

TABLE III. TUBAL STERILIZATIONS (MADLENER PROCEDURE)

OPERATOR	YEAR OF PUBLICATION	NUMBER OF CASES	FAILURES
Madlener	1919 and 1932	166	0
Weber (Munich)	1923	50	0
Schreiner, R.	1927	84	0
Baksecht (Russia)	1929	29	0
Eyding, A.	1933	63	0
Macke (Düsseldorf)	1933	21	0
Rubowits and Kobak	1934	75	4
Otto	1934	117	0
Sänger	1934	620	0
Koller, Waser, Frey Walthard (Zurich)	1934	1,500	8
Köhler (Hamburg)	1934	250	0
Holtermann (Cologne)	1935	250	0
Runge (Heidelberg)	1936	600	0
v. Graff	1936	147	1
Iowa Gyn. Clinic since July, 1934	1937	157	0
15 Reporters		4,279	13 = 0.3%
Additional failures reported			6
			19 = 0.44%

The Madlener technique has been successful in 99.6 per cent.

There is somewhat less than 100 per cent success. It is to be expected that the 0.3 per cent failures can be reduced further if not entirely eliminated by technical proficiency.

Although it may be assumed that the cases reported in the literature have been properly followed up, exact data as to the time elapsed since the operation have not been recorded. The 147 cases of my own experience have been followed up for four and more years, and the additional 157 cases of the Iowa Clinic, from two to four years.

In Table III, I have conscientiously included six failures reported in the literature without their counterbalance of successful cases. Adair has seen two cases, Döderlein, one, of uterine pregnancy following Madlener sterilization in the course of a cesarean section, while

the pregnancy was located in the Fallopian tube of the three cases mentioned by Goldschmidt, Heimann, and Hüssy. Even with the addition of these six failures, there is only one failure in over 200 sterilizations by this method.

Before discussing the failures in relation to surgical technique, I want to point out, as a possible source of disappointment, that the patient may be pregnant at the time of operation. I have seen a woman who denied having had intercourse because she thought the operation would do away with a possible pregnancy. Actually, she had conceived nine days before operation.

It is likely that other of the reported failures had the same origin. Therefore it is advisable to do a curettage if there is any doubt of the reliability of the patient's statements. Operation even immediately following menses does not exclude the possibility of an early pregnancy.

Another source of failure which has nothing to do with the actual technique of the ligature is the confusion of the Fallopian tube with the round ligament. Köhler first warned against this error and Schultze has reported a case in which the ligature was actually placed on the round ligament by mistake.

In the vaginal performance of the Madlener procedure, I well understand how this may happen and there is every reason to believe that the single failure among my own cases was due to this error. Especially in teaching, it is necessary to emphasize this pitfall.

Failures due to technique fall into two principal categories: (1) The ligature, becoming loose, does not stay in the crushed furrow or the entire loop of tube slips out. This has been demonstrated by Fraenkel in his animal experiments, the salpingographic studies of Fuchs-Lark, Wolf, and Thiessen, and the relaparotomies of Koller and Otto; (2) The histologic examination of specimens (Rubowits-Kobak, Adair) has shown that the proliferating epithelium of the tubal mucosa may establish ducts or fistulas which circumvent the ligated area. In addition, communication may be re-established by its tunnelling through the scar tissue and opening a new tubal canal. I feel that the formation of fistulas is encouraged by laceration of the serous covering of the tube.

These mishaps may be avoided by taking a generous loop and by exercising care in the application of the crushing instrument. The security of the ligature is greatly increased by using nonabsorbable material and by carrying the suture through the mesosalpinx and tying it separately around each leg of the loop (Markowsky).

It is because of the possibility of the ligature's slipping that I do not favor cutting the tube as Pomeroy and others have advised. If the tubal loop is cut, careful peritonization is required. This complicates the procedure without giving additional advantages over the original Madlener.

With the observance of these simple precautions, the Madlener method should prove the most reliable means of permanent sterilization. Its simplicity and the absence of bleeding qualify it for vaginal performance.

In using the vaginal route, the Fallopian tubes can be approached in either of two ways: (1) anteriorly, after dissection of the bladder through the vesicovaginal fold, (2) posteriorly, through Douglas' pouch. A number of authors prefer the Douglas pouch route as routine procedure in vaginal hysterectomy. Burch recommends it in particular for tubal sterilization in order to circumvent possible difficulties in the dissection of the bladder.

Personally, my preference is for the incision of the vesicovaginal fold because of the ideal fixation of the uterus which can be obtained by placing a clamp on the round ligament. My preference for the vaginal approach is evidenced by the fact that I have used it among the 211 sterilizations of my own material, i.e., 64 by tubal wedge operation and 147 according to Madlener, but in 4 cases of sterilization in the course of cesarean operations.

Vaginal operation has numerous advantages. Primarily, it is in the best interests to the patient because it minimizes surgical risk, the dread of operation and the period of incapacity. The anesthesia is brief and the operative shock eliminated. Postoperative discomfort is negligible and the patient is usually up on the third day. In five to seven days, she is able to leave the hospital and resume her ordinary activities.

Involving no abdominal incision or resultant scar, the vaginal operation carries no suggestion of mutilation. This is of vital importance in reducing the psychic effects of sterilization. With the element of complete security, it is likely to improve the sex relationship and favor response. The patient's subsequent health is unimpaired and her psychic adjustment very likely to be improved. Considering the average income of our public, the saving of hospital days should be an important factor. Since the majority of sterilizations are among the needy and in those in public institutions, their performance by the vaginal route assumes great economic proportions.

The advantages of the vaginal performance of the Madlener hold equally true for a great number of gynecologic operations. By conservative estimate one-third of all pelvic surgery routinely performed by laparotomy can be efficiently accomplished by the vaginal route, with an average reduction of the hospitalization time of 50 per cent. This would not only mean a considerable economy of the entire costs of such operative gynecologic cases, but actually increase the capacity of the department. Therefore, both for medical and social reasons, the instruction in vaginal technique should be given more attention in our medical schools.

SUMMARY AND CONCLUSIONS

1. The tubal sterilization according to Madlener is recommended as the procedure of choice in the permanent sterilization of women.

2. The advantages of the original Madlener over other methods including the cornual wedge operation, are described.

3. 4,279 cases from the literature have proved successful in 99.7 per cent. This includes 304 cases reported for the first time by the author, with only one failure.

4. The causes of failure are pregnancy at time of operation, mistaking the round ligament for the Fallopian tube, slipping of the ligature, and lacerations of the serosa which encourage fistula.

5. The cutting of the tied loop of the tube is likely to invite failures and therefore should be omitted.

6. The advantages of the vaginal route in the performance of sterilization as well as pelvic surgery in women on the whole are emphasized.

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TYPHOID FEVER IN PREGNANCY*

Probable Intrauterine Transmission of the Disease

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TYPHOID fever is rare among pregnant women; only two such patients have been observed among more than 11,000 obstetric admissions to the University Hospitals between Jan. 1, 1926, and March 1, 1939. The case here reported is unique in that a woman convalescent from typhoid fever gave birth to a child presenting presumptive evidence of the intrauterine transmission of the disease. The presence of a positive agglutination reaction for typhoid in the blood and the recovery of the typhoid bacillus from the feces of the newborn child appears to warrant this presumption. This case report is of further interest because of the high content of H and O typhoid agglutinins in the breast milk and because of the carrier state of both mother and baby.

*Assistance on the bacteriologic aspects of the problem was furnished by Dr. I. H. Borts.

CASE REPORT

W. H. (No. 38-27918), a 21-year-old married white gravida ii, was admitted to the University Hospitals on Sept. 14, 1938.

This patient had been delivered spontaneously of a 2,400 gm. baby in this hospital in February, 1937. During the subsequent eighteen months there were several attacks of colic in the right upper abdominal quadrant. These pains radiated to the right shoulder blade. There was concomitant nausea and vomiting but no history of jaundice.

The menstrual history was normal. The last menstrual period began March 5, 1938, and the expected date of delivery was Dec. 12, 1938.

The onset of the present illness, two weeks before admission (thirty weeks after the last menses) was characterized by general malaise, low backache, sore throat, nausea, vomiting, chills, and persistent fever. There was no history of rose spots, diarrhea, tympanites, or epistaxis.

On admission the temperature was 103.8° F., the pulse rate was 140, and the respirations were rapid (40 per minute) and shallow. The patient was acutely ill, dehydrated, drowsy, and the speech, although coherent, was slow and thick. The pupils reacted to light, the thyroid was not palpable, and the lungs were clear to percussion and auscultation. The heart was not enlarged, and the rhythm was regular, but a faint systolic murmur was heard at the apex. The blood pressure was 110 systolic and 74 diastolic. The lower pole of the spleen was barely palpable. All the deep reflexes were present but diminished. There was no peripheral edema. The uterus, extending slightly above the umbilicus, was estimated to be the size of a six to seven lunar month pregnancy. Fetal heart sounds were not audible. The vaginal outlet was marital, well supported, and free of discharge. The cervix was soft and closed, and the vaginal mucosa was bluish in color.

Laboratory Findings.—The urine was normal, except for a moderate albuminuria. The red blood cell count was 2,700,000 and the hemoglobin was 10 gm. per cent (Haden-Hauser). The red cells showed some variation in size, shape, and staining qualities. The total leucocyte count was 10,000. A differential count revealed 66 per cent lymphocytes, 3 per cent monocytes, 28 per cent polymorphonuclear leucocytes, and 3 per cent unclassified leucocytes. The blood Wassermann and Kline reactions were negative. The blood showed positive agglutinins for *B. typhosus* in a dilution of 1/1280. Cultures from the urine, feces, and blood stream were positive while those from the colostrum were negative for typhoid.

Course in the Hospital.—The course of the patient was rather stormy for the first week after admission, but the temperature gradually reached normal on September 30 and thereafter was not elevated.

From September 26 to 30, there was a transient bilateral mastitis which was treated conservatively. Albumin was not present in the urine after October 2. The bile, which was obtained through a duodenal tube, and the stools continued to show typhoid organisms (see Table I). On December 29, following a seven-hour labor, the patient was delivered spontaneously from L.O.A. position of a living, male infant, weighing 2,745 gm. The puerperium was afebrile. On Jan. 2, 1939, the breast milk agglutinated typhoid bacilli in a dilution of 1/1280. Five days later, the centrifuged whey produced agglutination in dilutions of 1/5120 and 1/2560 for the O and H antigens, respectively. A cholecystogram (oral dye) on Jan. 13, 1939, revealed a poorly functioning gall bladder containing several stones. Following cholecystectomy on Feb. 2, 1939, typhoid bacilli were demonstrated by culture in the mucosa of the gall bladder. The stools obtained after February 20 did not contain the organism.

The mother handled the infant once shortly after birth for approximately twenty minutes. The child's course was not unusual except that *B. typhosus* has been cultured repeatedly from the stools. The blood serum agglutinated the H antigen at a dilution of 1/640 on the second and ninth days, at 1/160 on the thirty-ninth, and at 1/80 on the sixty-third day of life. The agglutination test for the O antigen and attempts to grow *B. typhosus* from blood clot cultures on three different occasions gave negative results. From the twenty-fifth to thirty-first day of life the baby had a fever of 100° to 102° F. and a rash simulating miliaria rubra. It was believed, however, that the temperature elevation was due to a moderately severe

reaction from vaccination for smallpox. Again on the fifty-first to fifty-fifth days of life the temperature ranged between 101° and 104° F. Nothing was found on physical examination to explain this rise. The baby was discharged from the hospital at the age of 64 days.

Follow-up.—Subsequently, information was obtained that the baby on the seventy-fourth day of life had a sudden rise in temperature to 104° F. with signs of colic, which persisted for a few days. At the age of ninety-two days it was apparently well, having approximately doubled its birth weight.

TABLE I. BACTERIOLOGIC STUDIES ON W. H.

DATE	FECES	URINE	BLOOD	BILE BREAST MILK	BLOOD AGGLUTINATIONS	MILK AGGLUTINATIONS	REMARKS
9/13/38			+		1/1280		
9/15/38	+	+	+		1/1280		
9/16/38	+	+	+				
9/17/38 to 10/27/38	+	+					Nine cultures made from the feces and two from the urine during this interval
10/31/38	+	-					
11/ 4/38				+	1/1280		
12/20/38	+						
12/29/38	Spontaneous delivery						
1/ 2/39				-		1/1280 (whole milk)	
1/ 6/39							Culture from cervix + for *B. typhosus*
1/ 7/39		-	-		O = 1/2560 H = 1/640		
1/ 9/39						O = 1/5120 H = 1/2560 (whey)	
2/ 1/39	Cholecystectomy: The mucosa of the gall bladder was (+) for *B. typhosus* while the appendix was (-)						
2/ 2/39	+						
2/ 7/39					O = 1/320 H = 1/640		
2/ 8/39	+	-					
2/15/39	-						
2/20/39	+						
2/21/39 to 2/27/39	-	-					Four cultures made from the feces and one from the urine
3/ 2/39	-				O = 1/320 H = 1/1280		

Pathology.—The gross specimen consisted of a gall bladder which had been opened and fixed in formalin. When spread out, it measured 8 by 6 cm. The serosal surface was somewhat ragged, but in the center there was a smooth strip of peritoneum, which was free from adhesions. The wall was slightly thickened. There was no evidence of acute inflammation. The mucosa was intact. Ten small brown stones accompanied the specimen.

Microscopically the wall of the gall bladder was slightly thickened and infiltrated by chronic inflammatory cells. The epithelial lining was intact.

Histologically the appendix showed mild chronic inflammatory changes in the wall of a nonspecific type.

Diagnosis: (1) "Chronic cholecystitis and cholelithiasis." (2) "Mild chronic appendicitis."

Epidemiology.—The State Epidemiologist reported that the patient lived in a small village and that the family obtained milk from their own cow. They used an outdoor toilet and shared the use of a well with another family. The well, covered with planks, was not situated in a depressed or low area. The patient ate food identical with that eaten by other members of the family: the husband, a son, and a brother. The husband was admitted to the University Hospitals on Oct. 3, 1938, treated for typhoid fever, and later discharged as a typhoid carrier. The brother was sick for a period of six weeks in October and November. It was reported that he had influenza, but it is probable that he may have had typhoid fever. The son is not known to have been infected.

LITERATURE

Lynch[1] reported a typhoid fever incidence of 2.8 per cent among pregnant women admitted to the Johns Hopkins Hospital, and Freund[2] recorded an incidence of 1.28 per cent from 10 of the larger European cities.

Pregnancy evidently does not alter the prognosis of the disease. Hicks and French,[3] in 1905, reported a maternal death rate of 14 to 17 per cent but emphasized the fact that the effect of the disease on pregnancy is bad, as abortion or premature labor occurred in the majority of cases. Morse[4] summarized the factors which have been advanced to explain spontaneous premature interruption of the pregnancy and considered the most important to be: (1) the absorption of toxins by the fetus, and (2) intra-uterine typhoid fever resulting in fetal death.

Seventy-eight case reports of typhoid fever occurring during pregnancy were collected from the literature (Lynch;[1] Hicks and French;[3] Morse;[4] Griffith and Ostheimer;[5] Ratliff;[6] Rosensohn;[7] Ferri;[8] Laffont and Mèle;[9] Wing and Troppoli;[10] Patoir and Gelle,[11] and Sai[12]). In 18 cases the details were incomplete and the diagnosis may well have been erroneous, since they occurred before the Widal agglutination test was perfected. Among the remaining 60 satisfactory cases, 29 developed the disease before the period of fetal viability. Five of these women eventually went to term and were delivered of living mature babies. The other 31 women, in whom the disease appeared during the last trimester of pregnancy, were also delivered of living infants but only 17 of their babies survived longer than four days. In one case *B. typhosus* was demonstrated in the lochia.

Klein[13] in 1911 presented evidence that in the majority of cases the immunity in the baby was passive; agglutinins pass through the placenta from the mother to the infant. In all of those cases collected from the literature, the serum reaction was negative and typhoid bacilli could not be isolated from the spleen, bone marrow, liver, etc., at autopsy in the fetuses where the intrauterine exposure to the disease had been less than three weeks. Presumably, the placenta acts as a temporary barrier. Morse was of the opinion that the infant was not affected until damage had occurred to the placenta. Bolton[14] described the different pathologic changes appearing in infants before and after birth. Those infected in utero had no demonstrable lesions in the gastrointestinal tract, whereas in postnatal infections such lesions were prominent, as in adults. He was of the opinion that neonatal infections were due to mouth contamination while prenatal infections were probably by way of the blood stream.

The Widal reaction, which was recorded in 38 out of 79 infants, was positive in 17 (included a set of twins) and negative in 21. In the other 41 cases the reaction was not reported. In one of those having a positive Widal reaction, typhoid bacilli were noted in the wall of the umbilical cord, and in another the typhoid organisms were isolated for the first time from the stools. The authors, who reported the latter case, were of the opinion that the baby formed its own agglutinins.

COMMENT

Approximately 2 per cent of all individuals having typhoid fever remain carriers, the causative organism usually persisting in the biliary system or the intestine. In the family here recorded three carriers were found. In one (mother) the organism was in the gall bladder, in another

(father) localization had occurred in the gastrointestinal tract but was proved not to be in the biliary system, and in the third (baby) the location was not established. The condition noted in the mother confirms the observations of Boyd[15] and Borts[16] that over 95 per cent of typhoid carriers have chronic cholecystitis often associated with stones. The carrier state, in the infant presented, may be due either to localization of the bacilli in some part of the intestinal tract or in the biliary system. If it is assumed that Bolton's hypothesis is correct, the latter site seems the most probable.

All other authors have found the agglutinin content in the breast milk to be low. By using the method described by Hall and Learmonth,[17] who observed that the fat in milk interferes with the agglutination reaction, and, therefore, made tests on the whey, our results showed much larger quantities of both O and H agglutinins in the milk than in the blood. Newman[18] has noted similar reactions in cows with undulant fever. He was of the opinion that the protein fraction of the blood serum, which carried these immune bodies, became concentrated and stored in the colostrum. It was also demonstrated that if newborn animals were given colostrum rich in antibodies, the recipient's blood serum will in a few hours show a positive reaction against malta fever. Such was the experience of Talamon and Castaigne[19] who reported a woman developing typhoid fever four months post partum. The baby was allowed to nurse from the breast for the first month of the disease. It was then weaned for a few weeks. Subsequently breast feedings were resumed. They noticed that as long as the baby took breast milk the blood showed a positive Widal reaction, but a few days after discontinuing the breast milk the Widal reaction became negative.

On the night following birth, the baby, here described, was taken to breast by mistake. It is possible that the positive Widal reaction of the baby's serum reported shortly after nursing could have been due to absorption of agglutinins from the colostrum. However, it is the opinion of the authors that this exposure had very little to do with the persistently positive reaction of the serum and that the infant produced its own agglutinins.

Although the baby went to breast only once, in this particular case, there did not seem to be any contraindication to breast feeding. If the mother were a carrier and the baby had no evidence of infection, weaning would seem to be desirable.

SUMMARY

A case of probable intrauterine typhoid fever in a baby born of a mother convalescent from typhoid is described. The principal observations of significance were: the high agglutinin content of the breast milk against typhoid fever; the presence of typhoid bacilli in the baby's stools; and the carrier state of the mother and baby. Typhoid organisms were found in the maternal bile obtained by duodenal drainage. Cholecystectomy was performed during the fifth post-partum week. The gall bladder contained stones and typhoid bacilli were cultured from the mucosa. In all probability, the infant formed its own agglutinins.

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WATER EXCHANGE AND SALT BALANCE IN HYPEREMESIS GRAVIDARUM

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WHATEVER the basic cause, vomiting occurs in a large proportion of pregnant women. Persistent vomiting, with extensive loss of water and chlorides, leads primarily to dehydration and alteration in the electrolyte pattern of the extracellular fluid and secondarily to starvation. Approximately 70 per cent of the body weight is made up of water. Fifty per cent is intracellular and 20 per cent extracellular. The extracellular water is divided into interstitial water and blood plasma. The interstitial water, including lymph, represents 15 per cent of the body weight. The vascular fluid accounts for approximately 5 per cent of the body weight. Body water holds electrolyte in solution, and changes following loss of electrolyte may be serious.

Lashmet and Newburgh[1] found that normal individuals need approximately 500 c.c. of urine water to permit the kidneys to excrete all urine solids. If the urine volume falls below this amount in normal individuals, retention of urine solids will result. In renal disease they found that as the concentrating ability was lowered more urine water was necessary to remove all urine solids. They calculated the loss of water through the skin and lungs. This was called water of vaporization. Vapor water is always expended even though there is a shortage of urine water. To be reasonably certain that the kidneys are permitted sufficient water to excrete all urine solids presented to them, Newburgh[1] and Maddock and Coller[2] found that the individual should have the following needs supplied:

Vapor water	1,000 c.c.
Urine water	1,500 c.c.
Stool	200 c.c.
Total	2,700 c.c.

Plus any abnormal loss.

In their dehydration experiments Maddock and Coller[2] found that normal individuals will retain urine solids if the urine volume is below 500 c.c. in twenty-four hours.

Gamble[3] described the changes in electrolyte due to abnormal losses of body fluid. When vomiting is present several factors must be considered. The body loses water and electrolyte and may suffer from starvation. If the water loss is great there is not sufficient urine water to excrete all urine solids presented to the kidneys. As gastric juice is composed chiefly of HCl, persistent vomiting causes a serious loss of chlorides. Chloride ions are lost in excess of sodium ions. The structure of the blood plasma and interstitial fluid is almost identical, each containing sodium as the chief cation and chloride and bicarbonate as the chief anions. With a loss of chlorides, as in vomiting, there is a compensatory mechanism which increases the bicarbonate proportion. This tends to produce a state of alkalosis, or if the pH is normal, a compensated alkali excess will occur if chlorides are lost and if the individual is able to maintain a water intake sufficient to permit the kidneys to excrete all of the urine solids presented to them. Because no renal impairment exists there will be no increase in blood urea or nonprotein nitrogen. The carbon dioxide combining power will be increased.

If the fluid intake is too small to permit the kidneys to excrete all urine solids, some will be retained. This produces a further change in the electrolyte structure of the extracellular fluid. Some of the space formerly occupied by chlorides will be replaced by the retained urine solids as phosphates, sulphates, and inorganic acids. The increase in bicarbonate will be less than in the individual excreting all urine solids.

In the presence of starvation ketone acids form. As they are carried in the same compartment as chlorides and bicarbonate, some bicarbonate will be displaced. A positive acetone test in this instance indicates a ketosis, not an acidosis.

HYPEREMESIS GRAVIDARUM

Peckham[4] reported the laboratory findings in 60 cases of hyperemesis gravidarum. His findings agreed with those of Dieckmann and Crossen[5] and others. The records studied were grouped as mild and severe. In the mild cases there was no great change in the blood nonprotein nitrogen, or uric acid. Chlorides were reduced. There was an increase in the carbon dioxide combining power in some, in others a decrease. In the severe cases there was a marked increase in the blood nonprotein nitrogen and uric acid, the chlorides were greatly decreased and the carbon dioxide combining power varied from a marked increase to a marked decrease.

As chlorides are lost clinical symptoms quite similar to those noted in hyperemesis gravidarum develop. The most prominent are weakness, vomiting, drowsiness and finally even twitching and coma. It is, therefore, logical to assume that, as plasma chlorides are always decreased when vomiting of pregnancy is severe, the condition could be improved by the addition of chlorides. If renal function has been impaired by dehydration, fluids must be forced. A logical treatment for hyperemesis gravidarum is as follows: (1) Improve renal excretion, (2) restore a normal electrolyte structure, (3) remove abnormal ketone acids, and (4) maintain a normal fluid and acid-base balance.

Improve Renal Excretion.—In extensive dehydration renal function is impaired as a result of marked concentration of urine solids. Isotonic

dextrose solution, rapidly oxidized when given intravenously, provides an excess of water which makes it possible for the kidneys to excrete urine in a normal fashion. As urine solids will have been retained for some time in persistent vomiting, a large amount of urine water is desirable. In addition to the requirements for replacement of electrolyte, sufficient isotonic dextrose should be given to insure a twenty-four-hour urine output of 3,000 c.c. This large urine output will restore adequate renal efficiency and as a result the kidneys may regulate the excretion of excess substances in the body fluid. By giving isotonic dextrose in sufficiently large quantities, renal impairment will be overcome and retained urine solids will be excreted. This is an important step in the restoration of a normal electrolyte structure.

Restoration of Normal Electrolyte Structure.—There is a considerable shortage of chlorides when vomiting has persisted for some time. Coller[6] and associates found the low level of normal plasma chlorides to be about 560 mg. per 100 c.c. Coller states that death may occur when the plasma chlorides fall to approximately half the normal level. Mild symptoms are present when the plasma chlorides drop to 500 mg. per 100 c.c. and serious symptoms when they are around 400 mg. per cent. Normal saline contains 8.5 gm. of salt in each 1000 c.c. of water. When equal amounts of sodium and chloride are given, the kidneys must excrete excess sodium in order to allow the body fluid to retain needed chlorides. It is important to restore the excretory power of the kidneys if the electrolyte structure is to be repaired by the addition of sodium chloride.

The amount of sodium chloride necessary to restore normal plasma chlorides must be determined. If the replacement is inadequate, vomiting will persist and there will be a continued loss of chlorides. Coller[6] and associates have developed an ingenious formula for determining the amount of salt necessary to raise the plasma chlorides to a normal level. They found that for each 100 mg. per 100 c.c. that the plasma chlorides were to be raised, 0.5 gm. of sodium chloride should be ingested for each kilogram of body weight or 0.2 gm. of sodium chloride for each pound of body weight. Using this formula, it becomes a simple matter to restore salt and if the kidneys are excreting well, a normal electrolyte structure will result.

Remove Ketone Acids.—Salt solution cannot remove ketone acid bodies if they are present. As dextrose is oxidized the ketone acids will be destroyed and removed from the body fluids. It is therefore important to supply dextrose to overcome ketosis as well as to correct renal impairment. As isotonic dextrose liberates more free water it is used in preference to hypertonic glucose.

Maintain a Normal Fluid and Acid Base Balance.—As the plasma chlorides are restored and as renal excretion is improved, the patient will show marked clinical improvement. Symptoms will recur if chlorides are lost and dehydration develops. Coller[6] states that at least 4.0 gm. of sodium chloride should be ingested daily in addition to any lost by abnormal routes. The urine output should exceed 2000 c.c. daily. Five hundred cubic centimeters of normal saline each twenty-four hours

will furnish an adequate amount of salt if the plasma chlorides have reached normal limits, providing there are no abnormal losses. If vomiting persists, the emesis should be measured and an equal amount of normal saline added to the basal requirement for that twenty-four-hour period. Isotonic dextrose is then given in amounts sufficiently large to furnish a daily urine output of between 2000 and 3000 c.c. Isotonic dextrose will supply a low caloric intake and in addition maintain an adequate renal excretion.

As the signs and symptoms resulting from hypochloremia disappear, the patient will usually retain small frequent feedings. Soluble phenobarbital in small amounts subcutaneously, or phenobarbital by mouth will provide adequate sedation.

MILD VOMITING OF PREGNANCY

Mild vomiting occurs in about 50 per cent of all pregnant women. To prevent hyperemesis gravidarum these patients must be treated. The only serious early defect produced by vomiting is a loss of body chlorides. Most patients can replace chlorides if properly instructed. The ordinary 00 gelatin capsule will hold 1.0 gm. of NaCl. This amount of salt taken with approximately two-thirds of a glass of water will furnish volume for volume replacement of chlorides lost by vomiting. Salt is retained readily when taken in capsule form. Salt must be accompanied by water to permit the body to retain it. In addition to salt replacement, enough water must be ingested to maintain an adequate urine output. Most patients can drink sufficient fluid to enable them to excrete three pints of urine in each twenty-four hours. It has been possible following this regime to prevent persistent vomiting if treatment is started early. The patients are instructed to eat small, low fat meals frequently. Mild sedation is obtained by giving phenobarbital two or three times daily in half grain doses.

COMMENT

The reported blood chemistry findings in hyperemesis gravidarum indicate that the mild cases have a slight reduction in plasma chlorides, with little evidence of nitrogenous retention. Patients with persistent vomiting reveal a marked reduction in plasma chlorides, and give evidence of nitrogenous retention. Glassman[7] reported an average plasma chloride value in hyperemesis gravidarum of 489 mg. per cent and considered this reading essentially normal. Peters and Van Slyke[8] and Bartlett, Bingham and Pedersen[9] report normal plasma chloride values to be between 560 and 630 mg. per cent. Bartlett and others emphasize that when plasma chloride values are as high as 500 mg. per cent, symptoms of hypochloremia will be present in some patients. They warn that any loss of electrolyte and water is important and must be replaced if the chemical processes of the body are to be efficient.

The cause of hyperemesis gravidarum is not known, but it is known that there is a reduction in plasma chlorides with an alteration in electrolyte structure. As vomiting persists, dehydration develops, urine volume decreases, renal impairment occurs, and retention of urine solids takes place. Teitelbaum[10] has found that there is no direct relationship

between low plasma chlorides and azotemia, but that the frequent association is brought about by two conditions, vomiting and inadequate urine volume.

A practical treatment should be simple. If the plasma chloride values are known, the amount of salt necessary to restore normal plasma chlorides may be calculated by using Coller's[6] formula. Gamble[3] found that it was unnecessary to use an elaborate solution to replace electrolyte, as all extracellular ions except sodium and chloride ions will be supplied by the metabolic processes even in starvation. To make this possible, the kidneys must be able to control the internal environment with normal efficiency. For this water must be available. Salt may be supplied by the intravenous injection of normal saline. Five per cent dextrose given intravenously will furnish the kidneys with sufficient water to remove retained urine solids, and as the dextrose is oxidized, ketone acids, if present, will be destroyed. Isotonic dextrose is to be preferred as no dangerous symptoms have been noted following its use. Warthen[11] found that no dogs died following experimental infusion of normal saline or 5 per cent dextrose but that frequent fatalities resulted following the use of 10 per cent dextrose. DeLee[12] reported collapse in two cases following the use of hypertonic glucose. After chlorides are replaced and normal renal function is restored, sufficient salt must be given to maintain normal plasma chlorides and sufficient fluid must be ingested to maintain adequate renal function.

The serious symptoms of hyperemesis gravidarum may be entirely due to a disturbed electrolyte structure and dehydration. Many investigators have advised the use of sodium chloride. Coller has developed a clinical rule which permits accurate calculation of the salt deficit. This formula works well in hyperemesis gravidarum; the plasma chlorides may be brought to a normal level in a few hours. This rapid improvement has not been noted if salt replacement is inadequate. The administration of salt solution alone is not sufficient. Glucose and water must be given in sufficiently large amounts to permit restoration of normal renal function. As the kidney function is then unimpaired, excess ions may be excreted. Thus if sodium is given in excess of the body need, the excess sodium may be excreted. Rapid improvement has resulted following this treatment. Clinical improvement may be maintained by supplying an adequate amount of salt and water to satisfy the daily requirement.

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THE TIME OF OVULATION IN THE HUMAN FEMALE

As Determined by the Measurement of the Hydrogen Ion Concentration of Vaginal Secretions

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THE marked periodic change in the flora of the vaginal canal together with the cyclic changes in the vaginal smears suggested to us the possibility that the hydrogen ion concentration of the vaginal secretions might have a characteristic menstrual cycle pattern.

Many studies of vaginal secretion pH have appeared. Most of these are the result of an interest in the bacteriology in normal and pathological vaginae.

Behrens and Naujoks[1] reported that the vaginal secretions are quite acid in nonpregnant and pregnant women, and that some pathologic conditions, notably gonorrhea and carcinoma, yield a less acid pH. They reported consistent readings below a pH of 7.0, the range in normal women being from 3.86 to 6.84. No cyclic changes were mentioned. Guthman and Koch[2] reported essentially the same findings. They observed pH's consistently higher than those of Behrens and Naujoks, varying between 5.0 and 7.0. Guthman and Koch also observed that a rise in pH occurred just before the menstrual flow. Oberst and Plass[3] reported that the pH of the vaginal secretions varies directly with the type of bacterial flora present and, therefore, due to the change in flora during the menstrual cycle a corresponding change in pH is to be expected. They also reported that the pH found in different portions of the vaginal canal varies, the secretion from the upper portion (posterior) having a lower value than that of the secretion from the lower portion (anterior).

In the measurement of the pH of these secretions various methods have been employed. Sanssle[7] used litmus paper, Behrens and Naujoks used an electrometric method, Guthman and Koch employed indicators, and Oberst and Plass made use of a microquinhydrone electrode. With the exception of Oberst and Plass who used samples of secretion from definite portions of the vagina, all others used some type of washing for the determinations.

In the present study six normal white women of childbearing age were observed daily for a three-month period, including three complete menstrual cycles. The vaginal washings of the first subject were studied colorimetrically using bromcresol green and chlorphenol red as the indicators. The others were studied using a glass electrode in a Hellige electrometric pH meter. In all subjects, the saliva and urine were also studied from the standpoint of pH changes, the basal body temperatures were taken, smears were made of the vaginal secretions, and any subjective symptoms of ovulation were recorded. In one subject urine samples were extracted and examined for sodium pregnandiol glucuronidate.

It was found that a small glass syringe with blunt nose and rubber bulb could be used to inject about 5 c.c. of normal saline into the vagina,

and then to withdraw the saline for pH measurements and smear examinations. Saliva was obtained by washing the mouth with about 5 c.c. of saline. The vaginal washings, saliva, as well as a urine sample were obtained shortly after the subject arose in the morning. The rectal temperature was taken at about the same time each day, immediately before arising in the morning.

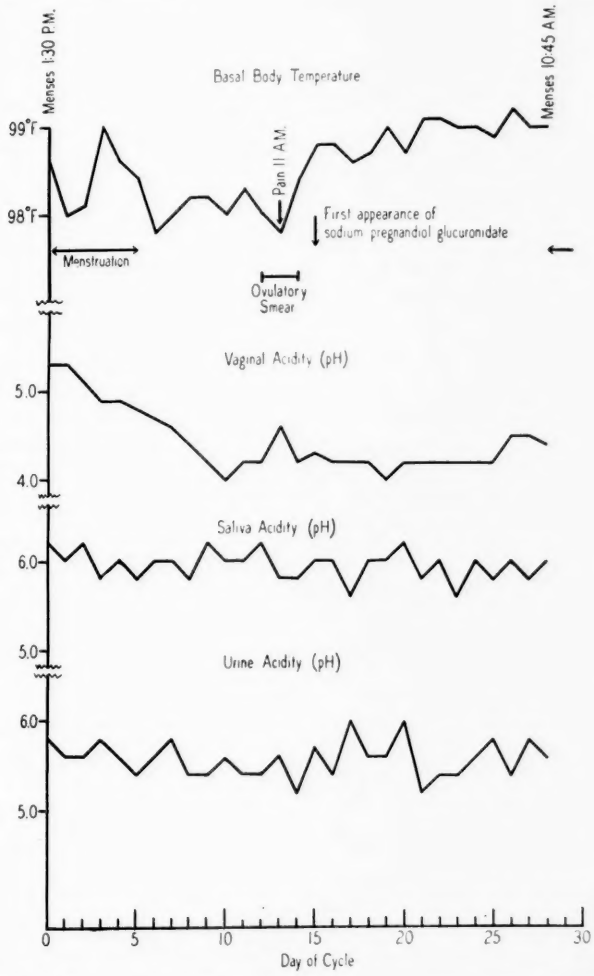

Fig. 1.—The daily record of the rectal body temperature taken before arising is shown at the top. Daily vaginal, salivary and urinary acidity appear as recorded during the menstrual month. The characteristic rise in pH of vaginal washing indicates the time of ovulation.

In the reading of the pH it was found that debris in the washings often caused a slightly higher reading than when the debris was allowed to settle. Thus the readings were always taken after the samples had settled in order to get constant values from determinations repeated over a period of three hours. By separate experiments we found that the saline washing can be diluted with an equal volume of saline without

changing the pH value, thus establishing the correctness of the surmise by Oberst and Plass. This observation supports the general supposition that the vaginal secretions are very well buffered. We conclude that the values obtained on the washings represent the average intravaginal condition.

The timing of ovulation by the basal body temperature has been reported by Zuck[9] and, together with our evaluations of smears as described by Papanicolaou[4] and amplified by Rubenstein,[6] give us what we consider the actual period of ovulation in our subjects. In cycles of three of the women subjective signs of follicle rupture were also observed.

The chart (Fig. 1) shows the pH readings of a typical menstrual cycle with correlated basal body temperature, smear evaluation, symptom of follicle rupture as well as pH values of the saliva and urine. Of 18 cycles studied in the 6 subjects, the essential features of this chart were repeated, although 3 cycles did not show such marked pH variations.

It will be noted that during the menstrual flow the pH values rise toward neutrality, and the value obtained varies with the amount of blood present in the flow. In most instances the pH then falls to a value near 4.0 to 4.2 which is maintained with slight variations up to the time of ovulation when a rise occurs to from 4.5 to 5.8. Following this rise the pH returns to the previous level of about 4.0 within twenty-four to forty-eight hours, and is again maintained with slight variations up to the premenstrual day or two, at which time the pH rises and reaches its peak during the first two days of the menstrual flow. In several of our subjects values of 7.0 were recorded during the heavy menstrual flow.

No significant fluctuations in the pH of the saliva or urine were observed so that the pH values of vaginal washings appear characteristic and have no apparent relationship to environmental factors.

It may be significant that the surface tension of the first morning urine shows a marked drop at the midmenstrual period from an analysis of the readings obtained by Perryman and Selous[5] although they did not associate it with the time of ovulation.

In the subject in whom sodium pregnandiol glucuronidate separations were made by the method of Venning[8] it was found in two cycles that the earliest appearance of this substance occurred in the second twenty-four-hour sample of urine following ovulation.

CONCLUSIONS

The pH of vaginal secretions shows a rhythmic variation with the menstrual cycle and has a characteristic rise at the time of ovulation.

There is a definite correlation between those changes in ovulation as indicated by vaginal secretion pH and that of basal body temperature and vaginal smear which we have reason to believe (Zuck, 1938) indicate the time of ovulation.

Sodium pregnandiol glucuronidate appears in the urine in the second twenty-four-hour specimen following ovulation. This was determined in two cycles.

The pH values of urine and saliva show no cyclic variations in women. The measurement of vaginal pH in our opinion affords a new method of timing ovulation.

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2109 Adelbert Road

THE EFFECT OF TEMPERATURE UPON THE VITALITY OF SPERMATOZOA

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IT IS accepted by Moench,[1] Belding,[2] and Hotchkiss, Brunner and Grenley[3] that the ideal temperature for viability of human spermatozoa outside the body is below room temperature and somewhere between 20° and 8° C. In a previous paper, I corroborated their findings, that spermatozoa live longer at lower temperatures than at higher temperatures.[4] However, spermatozoa in the course of their physiologic wanderings inside of the female never or rarely encounter lower temperatures than 37° C. The natural environmental temperature even in the scrotum rarely drops much below 37° C. Therefore to study motility, reaction to acidity, etc., of human spermatozoa at 8 to 20° C. or at room temperatures is not pursuing the study under physiologic or near physiologic conditions, and is comparable to studying the sex life of an Eskimo while in the tropics.

Human spermatozoa should be studied at body or scrotal temperatures in order to obtain a resulting truer picture. In testing for motility, viability, and endurance of human spermatozoa outside of the body, it would seem more logical to test their responses at their physiologic temperatures rather than at some subnormal temperature. Moreover, since it is accepted and recognized that spermatozoa are more resistant to cold than to heat, the endurance, motility, etc., should be studied at elevated temperatures rather than subnormal temperatures. A more exact physiologic status of the strength and resistance of the male elements can thus be obtained.

EXPERIMENTAL

Twenty-four young virile men between the ages of 20 and 38 were studied.* In most cases repeated examinations were performed. Seminal specimens were obtained

*The subjects included volunteer medical students, physicians, and private patients not complaining of sterility.

through masturbation and each specimen was divided into fractions and placed in small cotton-stoppered test tubes. One tube in each case was kept at room temperature while the others were incubated in small separate incubators, specially designed for the purpose, at various temperature levels. The incubators were exact to within one degree centigrade. The tubes were examined throughout the day and night by means of a platinum loop.

At the end of the experiments a mass of figures presented itself. No two cases were found to be alike. However, there was a surprising accordance of figures when allowed to be fitted into a normal range (Fig. 1). As was expected all the specimens at room temperatures showed optimal vitality. With increases of temperature, spermatozoal life became shortened. At 37° C. (body temperature) the average specimens endured from eight to ten hours, whereas at higher temperatures the spermatozoa died much more rapidly. The spermatozoa only lived from four to six hours at 41° C., while at 45° C. they were practically nonresistant.

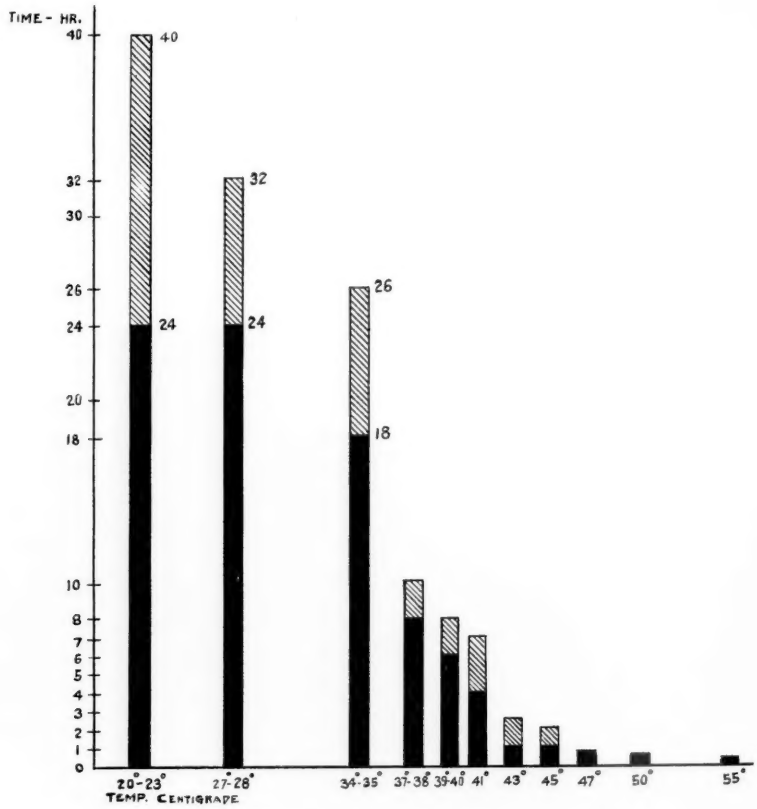

FIG. 1 EFFECT OF TEMPERATURE ON LONGEVITY OF SPERMATOZOA.

AREA REPRESENTS THE VARIATIONS MOST USUALLY FOUND.

Fig. 1.

DISCUSSION

Having obtained such uniformly similar results when testing normal spermatozoa for resistance to definite elevations in temperatures, I am now using these temperature reactions as part of my routine spermatozoal analysis. In general, if the seminal fluid conforms to most of the

other requirements of normalcy, the spermatozoa almost always endure for twenty-four to thirty-six hours at room temperature, and for eight to ten hours at body temperature, and for at least four hours at 41° C.

In the small series of cases tested so far, if I find that the spermatozoa in a specimen cannot endure room temperature for twenty-four hours, and body temperature for eight hours and 41° C. for at least four hours, then concurrent pathologic findings such as excessive abnormal forms, diminution in number, etc., are the rule.

SUMMARY

Human spermatozoa should be studied for motility and endurance, etc., at temperatures closely approximating their physiologic body temperature. Subnormal temperatures used to keep spermatozoa alive for longer periods of time do not reveal the true physiologic picture. The effect of elevated temperatures upon human spermatozoa was studied with the evolvement of a scale illustrating the normal longevity of spermatozoa at definite temperature levels.

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THE PREGNIOTIN TEST FOR PREGNANCY

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THE Arnold-Gruskin[1] test is a cutaneous test for pregnancy devised and developed by Dr. Benjamin Gruskin of Temple University. The substance used in our investigation is an antigen made from human placenta by E. R. Squibb & Sons, and distributed for experimental purposes under the name of "Pregniotin."

The test is an intradermal one. A positive reaction is evidenced by the appearance of pseudopodia. If pseudopodia fail to appear, the test is negative. Before testing with pregniotin each patient receives an injection of a control solution supplied with each package. This control solution, prepared from the amniotic membranes, is injected in exactly the same manner as the test solution itself, except that a separate sterile tuberculin syringe and needle are used. Any patient who shows a positive pseudopodic reaction to the control solution is not suitable for testing with pregniotin.

The technique as prescribed by the manufacturer is as follows: The skin of the forearm is cleansed gently with alcohol and dried with sterile gauze, care being taken to avoid producing erythema. Pregniotin and the control solution are drawn up in separate tuberculin syringes. The needle is inserted in the stratum spinosum layer

of the skin and very slowly and without using undue force, 0.1 c.c. of the control solution is first injected. The bleb so produced should be circular, and should present a typical pitted "orange peel" surface. In this series of cases, five minutes were allowed to elapse before the test solution was injected. If no pseudopodia were formed at the site of injection of the control test in this period of time, it was assumed that this patient was suitable for the use of pregniotin.

One-tenth cubic centimeter of test solution is then injected in a similar manner in a parallel location. If the reaction is positive, pseudopodia appear in one to four minutes, originating in the margin of the bleb. Within another ten minutes the entire reaction will have faded. If the reaction is negative, pseudopodia do not appear; the bleb remains circular and gradually regresses. The presence or absence of erythema is of no significance. The test should not be performed under artificial light, as pseudopodia, easily visible in daylight, may not otherwise be detectable.

The Gruskin test for pregnancy is said not to be applicable to patients who are jaundiced or have elevated temperatures. In patients who have received x-ray or radium treatment, two weeks are allowed to elapse before this test is applied. Patients who have been operated upon should not be tested until the incision is healed completely.

Gruskin[2] has reported results on a series of patients on whom the test was used under clinical supervision of Dr. J. O. Arnold at Temple University. In this series there were 162 correctly positive reactions, and 8 incorrectly positive reactions. The latter occurred in patients later found to be suffering from teratoid carcinoma or hydatidiform mole. There were 11 correctly negative reactions, 3 in the presence of carcinoma and of cervical erosions.

Schwartz[3] reported 221 cases in which the Gruskin test was employed. Correct diagnoses were arrived at in 209, or 94.6 per cent, and incorrect diagnoses in 12, or 5.4 per cent.

Pregniotin differs from the other materials[4, 5] used in cutaneous tests for pregnancy; the latter employ gonadotropic extracts of pregnancy urine, placenta, or pituitary. Pregniotin contains no gonadotropic substance. In the use of the gonadotropic extracts a positive reading is made when no cutaneous response is obtained. In the use of pregniotin a positive reading is made only when pseudopodia are found.

RESULTS

In our series reported here, 48 tests were made. Of these, 42 were females and 6 were males. The 42 females ranged in age from 18 to 48, with the greater number in the 18 to 30 age group. There were 11 patients who had had no children, 16 who had 1, 5 who had 2, 5 who had 3, and 5 who had more than 3. Of these 42, 22 were known to be pregnant clinically. Pregniotin gave positive tests in 21 of these 22 cases. The one negative result occurred in a patient who was six months pregnant, who had a positive Kline test and was under treatment for syphilis. Seven postnatals were tested, from one to thirteen days post partum. In all these cases the test was positive.

Three patients were examined for diagnosis:

1. Amenorrhea of two months. Obesity made a clinical diagnosis difficult. Pregniotin test was positive. The diagnosis of pregnancy was later confirmed clinically.

2. Pregnancy suspected because period was ten days overdue. Pregniotin test was negative. Examination revealed a lutein cyst.

3. Ectopic pregnancy suspected on basis of history. Pregniotin gave a positive result. Friedman test performed the same day was negative.

A series of 10 additional patients having the following gynecologic conditions, but having no clinical evidence of pregnancy, were likewise tested.

1. Chronic cervicitis and a retroplaced uterus. Pregniotin test negative.

2. Hysterectomy for pelvic inflammatory disease, seven weeks previous to test. Pregniotin test positive.
3. Pruritis vulvae being treated in the endocrine clinic. Pregniotin test negative.
4. Chronic cervicitis. Pregniotin test negative.
5. Fibrosis uteri and chronic cervicitis. Pregniotin test negative.
6. Multiple uterine fibroids. Pregniotin test negative.
7. Functional menorrhagia. Pregniotin test negative.
8. Functional menorrhagia with cervicitis. Pregniotin test negative.
9. Pelvic inflammatory disease, not operated on. Pregniotin test negative.
10. Chronic cervicitis. Pregniotin test negative.

Of the 6 males, ranging in age from 28 to 40, the first 4 were tested early in our series and all gave negative reactions. The last 2 were tested about four weeks after the expiration date of the experimental antigen supplied to us by E. R. Squibb & Sons. Both of these tests were positive. Each of the patients experienced pain and burning at the site of the injection, where a large wheal was formed. These false positives were probably due to deterioration of the antigen.

In no case in this series was a positive reaction obtained at the site of the control injection.

SUMMARY

1. A series of 48 patients were tested with pregniotin, an antigen prepared from human placenta for intradermal injection to determine pregnancy.

2. Pregniotin gave a positive reaction in 21 out of 22 patients known to be pregnant.

3. Seven patients, tested postnatally from one to twelve days post partum, all gave a positive reaction.

4. Six males were tested, 4 being negative and 2 positive. The 2 false positives were considered to be due to the deterioration of the product. No opportunity was afforded us of checking these results with a fresh product, as it was no longer available from the manufacturer.

5. Three patients examined for diagnosis by this test gave 2 correct results and 1 false.

6. Ten patients definitely not pregnant were tested, with 9 correct results and 1 false positive.

CONCLUSIONS

Pregniotin appears to be the best of all the skin pregnancy tests.

It does not, however, compare favorably with the Friedman modification of the Aschheim-Zondek test.

For a rapid, tentative diagnosis, pregniotin may prove useful, but results of this test should be checked by the Friedman method.

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THE CONTROL OF PAIN WITH LOCAL ANESTHESIA AFTER THE REPAIR OF EPISIOTOMIES*

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REPORTS of the successful use of soluble anesthetic solutions in rectal surgery with the purpose of relieving patients from post-operative pain have suggested the use of this type of medication following episiotomy and other perineal repair. The more or less widespread use of analgesia in labor has left the post-partum pain incident to perineal repair the most distressing factor of delivery and the puerperium.

This is merely a preliminary report on a small series of 25 patients with 25 alternate patients taken as controls. The results were so encouraging that it was deemed advisable to publish them. Two types of solutions were used, one an oil soluble solution of the following formula: Procaine base 1.5 per cent, butesin 6 per cent, benzyl alcohol 5 per cent, and oil of sweet almond q. s.; the other, an aqueous solution containing 1 per cent piperidinopropanedio di-phenylurethane hydrochloride.

TECHNIQUE OF ADMINISTRATION

Following repair of the episiotomy or perineal laceration 10 c.c. of the solution are withdrawn from the previously warmed bottle (110° F.) into a dry Luer Lok syringe. The skin of the area to be injected is thoroughly cleansed and an antiseptic applied. The solution is then injected slowly into the deeper tissue taking care that it does not go immediately beneath the skin or mucous membranes as it may result in sloughing. Following injection, massage of the parts assures an even distribution of the anesthetic and prevents pooling. The needle is inserted about ¼ inch on either side of the incision and the medicine then injected fanwise. The injection is made while the patient is still under the effects of the general anesthesia given during repair.

RESULTS

Patients were questioned regarding perineal discomfort upon awakening and on each post-partum day until discharge from the hospital. The variable factor or individual response to pain is definitely considered in evaluating the record. The water soluble solution was used in 10 cases. These patients were free from pain until the third or fourth post-partum day, at which time the effects of the anesthesia had apparently disappeared. They then experienced as much pain as the controls. The oil soluble anesthetic, however, kept patients for the most part entirely free from distress. Some degree of anesthesia remained in a few cases for as long as three weeks following delivery. The patients in whom no local anesthesia was used complained of varying degrees of distress, some of which was so intense that the application of anesthetic ointments or the use of analgesic suppositories per rectum was required.

In the series of 25 cases and 25 controls, healing did not appear to be impaired except in one instance. In this case there was a breakdown of the episiotomy wound requiring secondary suture. There had been noted an infected cervix, which could

*The butecaine was furnished by the Abbott Company.

not be treated adequately during pregnancy. The patient also had a mild postpartum pyelitis with positive *B. coli* urine culture. It would seem that one should not attempt the use of the infiltration in a situation such as this. Others, writing on the use of this procedure in rectal work, have stressed the inadvisability of using the solution in the presence of possible infection. There were no individual reactions or tissue sloughs; nor was there any delay in the healing of the wounds. In no case were there any general toxic effects noted.

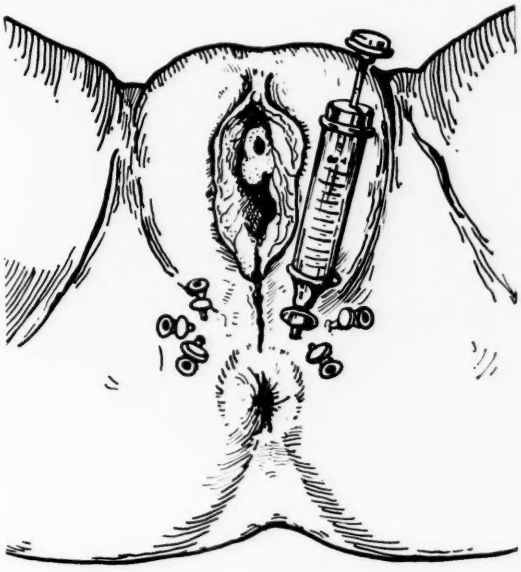

Fig. 1.

CONCLUSIONS

The results in this small series are very encouraging. With the more or less widespread use of analgesia in labor and with the desire of obstetricians to make labor and the puerperium as free as possible from distressing symptoms, it would seem that the use of slowly absorbing anesthetic solutions in repairs is a valuable adjunct to the obstetric armamentarium. The more slowly absorbed oil solutions appear from this study to be superior to the water soluble preparations. The presence of infection is a definite contraindication to the use of this type of procedure.

This being merely a preliminary study, a further evaluation will follow the continued use of the adjunct on a larger series of patients at some later date.

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THE FARGO CLINIC

HEART BLOCK AND PREGNANCY

Report of a Case, With Electrocardiographic Observations During Cesarean Section Under Cyclopropane Anesthesia

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THE following case is presented because of the unusual association of conditions. The number of reports of the occurrence of heart block and pregnancy is so small that additional observations on this association merit considerable study. A review of the literature reveals 13 reports of 15 cases.[1-13] Because of the scarcity of material the physician is confronted with a difficult problem in the handling of patients who present both these conditions.

In all but a few of the reported cases electrocardiograms have been taken before and after delivery, but so far as is known this is the first instance in which electrocardiograms have been taken during cesarean section.

CASE REPORT

The patient, E. L., white female, 33 years of age, housewife, pregnant for eight months, was admitted to the Mount Vernon Hospital on March 10, 1936, because of premature rupture of the membranes.

Her previous history was of considerable importance and interest, and the following were the essential facts. In childhood she suffered with measles, mumps, pertussis, and chicken pox. Tonsillitis occurred about twice a year between the ages of 18 and 22. In 1930 she came to this country from Ireland and was examined by immigration physicians, no defects being found then. Her menses began at 13 and have been regular. She has been married for six years and her husband has been in good health. In October, 1931, she became pregnant for the first time and attended the prenatal clinic at the Mount Vernon Hospital. She felt well until about May 1, 1932, when she began to develop symptoms and signs of eclamptic toxemia. In spite of rest in bed and routine treatment her blood pressure rose sharply. The signs of toxemia increased and the patient was admitted to the hospital on June 4, 1932. A four-and-one-half-pound premature baby was delivered which failed to survive the first twenty-four hours. At the time of admission to the hospital it was noted that the patient had a cardiac arrhythmia. On physical examination she presented definite signs of mitral stenosis and insufficiency with auricular fibrillation. No electrocardiogram was taken until five days later when the heart became very slow and regular. A record then showed complete auriculoventricular dissociation. The patient remained in the hospital until July 1, 1932, her convalescence being marked by a thrombophlebitis of the right long saphenous vein. After discharge from the hospital she made a slow but steady recovery, her blood pressure gradually becoming lower and the urine returning to normal. From time to time she experienced some precordial pain. Her menstrual periods were resumed in November, 1932. By April, 1934 the patient felt quite well and was able to carry on all her household duties without any signs or symptoms of cardiac insufficiency. Frequent electrocardiograms taken since 1932 showed a persistence of the heart block.

Her family history revealed that her father who is 65 years of age has hypertension. An uncle has a "bad heart."

Present History.—In September, 1935 the patient presented herself again, reporting that she had become pregnant. Her last menstrual period occurred on June 28, 1935. She was kept under constant observation during the antenatal period and bore the pregnancy extremely well. On March 10, 1936, approximately one month before term, her membranes ruptured spontaneously and she was admitted to the Mount Vernon Hospital immediately.

Physical Examination.—Temperature 99° F., pulse 48, respiration 20, blood pressure 170/80. Examination of the heart revealed the apex impulse in the fifth left intercostal space in the midclavicular line; no shocks or thrills palpable. The first sound at the apex was obscured by a loud rough systolic murmur. The lungs were clear. The fundus was about four fingerbreadths below the xiphoid. By abdominal palpation a diagnosis of left occiput anterior was made, with head floating. No vaginal examination was made. There were marked varicosities of the vulva and lower extremities.

Course in Hospital.—On consultation with Dr. William T. Liccione it was decided that because of the heart block it would be more expedient to perform a cesarean section than to risk a prolonged dry labor in a patient who had had a toxemia, and who now had an organic though asymptomatic heart lesion.

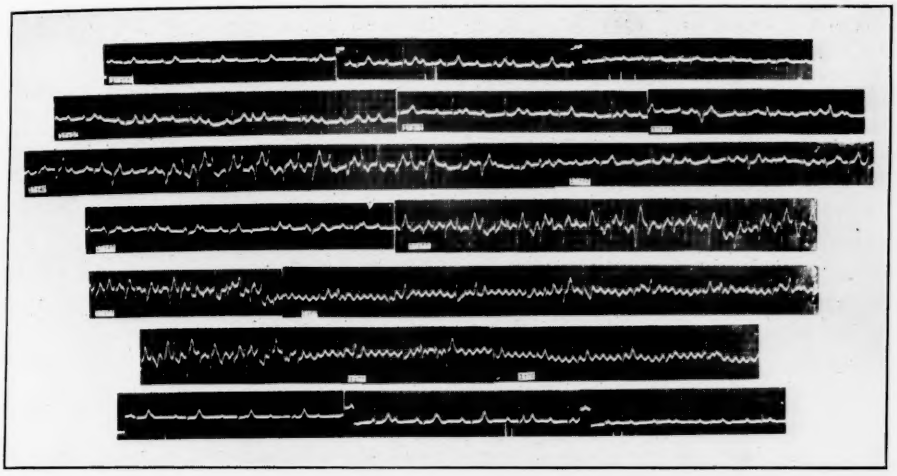

Fig. 1.—Shows record before, during, and after operation. At the top is seen three conventional leads of the control record; then a series of strips taken during operation using Lead II only. At the bottom is seen three conventional leads taken twenty-four hours after operation. The time each strip was taken is noted. 12:25, Control record, complete A-V dissociation, auricular rate 100, ventricular 50. 12:30, Occasional premature beat. 12:36, Premature beats from more than one focus. 12:40, Bigeminy, followed by ventricular extrasystolic tachycardia. 12:43, Premature beats. 12:47, A-V dissociation, ventricular rate 55. 12:52 and 12:56, Extrasystolic tachycardia. 1:00, Auricular flutter, premature beats. 1:05, Extrasystolic tachycardia, followed by flutter. 1:08, Auricular flutter.

The patient was examined by Dr. Wilmer S. Wilson, who decided to use cyclopropane anesthesia, first, because of the possibility of administering a high concentration of oxygen, and second, because of its assistance in contracting the uterus after the placenta is removed. As a preliminary, 3 gr. of pentobarbital were administered.

Low cesarean section was performed by Dr. William T. Liccione. The anesthesia was started at 12:27; the incision made at 12:37; the fetus delivered at 12:42; the operation completed at 1:15 A.M. During the course of the operation frequent electrocardiographic tracings were taken. These are shown in Fig. 1.

On leaving the operating table the patient showed some cyanosis which persisted for twenty-four hours. The pulse rate varied between 40 and 60. The further course was marked by the occurrence of low grade fever, due to thrombophlebitis, which began about three days postoperatively and lasted for about two weeks, running between 99° and 101° F. The patient, however, was free of symptoms and merely showed the presence of a small thrombus in the left long saphenous vein and one in a vein on the left side of the vulva. These disappeared within three weeks. Two weeks postoperatively the patient was sent home, and one week later was permitted out of bed. Examination three weeks postoperatively revealed

firm union of the wound, temperature ranging around 99° F., pulse around 50, blood pressure 150/70. The heart revealed sounds of good quality, the murmur heard before operation having disappeared.

Frequent examinations, both clinical and electrocardiographic, have been made since the patient left the hospital. Up to the present time, two years after operation, there have been no changes in the patient's condition. Her cardiac reserve is excellent and electrocardiographic tracings show the same mechanism as before delivery.

DISCUSSION

Lennox, Graves and Levine[15] who were among the first to record electrocardiographic tracings on patients during operation, stated that in order to understand the function of the heart it would be very important to study it during periods of stress. Our patient admirably presented such an opportunity, especially in view of the pre-existing disturbance of rhythm. It is difficult, however, to be certain that there is any one factor which is responsible for the changes recorded. In order to draw definite conclusions as to cause and effect, a large number of cases will have to be studied, varying only one factor at a time. Kurtz, Bennett and Shapiro[14] likewise encountered considerable difficulty in determining whether the surgical procedure or the anesthesia itself was the most important factor in the production of the disturbances which they recorded. In the series of the latter, the electrocardiographic tracings of their Case II appear to be identical with those which we obtained at 12:40, 12:52, 12:56, and 1:05.

It is known that two types of mechanism are found during Stokes-Adams seizures; one is complete ventricular standstill, the other ventricular fibrillation. The fascinating studies of Schwartz and Jezer[18, 19] have brought out some unusually interesting facts in this regard. Study of our records makes one wonder how far removed from ventricular fibrillation our patient might have been. However, it may be stated that in spite of the appearance of the records, the patient's condition on the operating table was never alarming, and at the completion of the operation it was as satisfactory as before.

Fig. 1 shows the electrical activity of the heart throughout the entire operative procedure. The development of the extrasystolic tachycardia and the auricular flutter in the presence of heart block is unusual and they are extremely important phenomena to report. It is to be hoped that more cases of this type will be described in the literature.

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58 South Second Avenue

THE PROBLEM OF IDIOPATHIC PURPURA HEMORRHAGICA IN PREGNANCY AND THE NEONATAL PERIOD

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THROMBOCYTOPENIC purpura occurs either as an idiopathic entity or as a symptomatic manifestation of blood dyscrasia, infection, exogenous or metabolic intoxication or secondary to malignancy.

The essential or idiopathic form first described by Werlhof[35] in 1775 is now regarded as dependent upon either (1) a primary defect in platelet formation (megakaryophthisis), (2) a pathologic destruction of platelets in the spleen, or (3) a qualitative disturbance in the platelets themselves.

The conduct and outcome of a pregnancy complicated by this disease is always problematical. Although splenectomy in definitely indicated cases improves the prognosis, the actual effects of purpura hemorrhagica upon the state of gravidity are uncertain.

Purpura in pregnancy and puerperium was first observed in 1765, but not until the establishment of the etiologic classification was proper attention directed to the morphology and coagulation of blood, as well as the capillary physiology. Mosher,[17] Rushmore,[28] and Pingat,[21] published clinical reports of this condition in pregnancy. More recently, Liebling[14] and Waltner,[34] described purpura in children born of thrombocytopenic mothers, but there is a dearth of completed records of this disease in the literature.

Pediatricians ascribe purpura in the newborn to heredity, while the obstetric writings subscribe to a congenital etiologic basis.

This report concerns itself with a severe idiopathic form of purpura hemorrhagica. Not only are clinical aspects presented but also a complete hematologic study of an infant, and its purpuric mother, before and after delivery. In addition, the surgical therapy (splenectomy), the striking absence of post-partum hemorrhage and the complete recovery of the mother are of an interest unusual enough to warrant the presentation of this rare condition.

G. R. (No. 42157), a 23-year-old primipara in the fifth month of pregnancy, entered Mt. Sinai Hospital on March 14, 1938, because of a four-day episode of continuous vaginal hemorrhage and a "gushing" epistaxis.

Menses (12x30x3) were always normal and regular, accompanied by slight dysmenorrhea. A chronic, discharging, bilateral otitis media with subsequent deafness resulted from an attack of measles, and four years ago a left mastoidectomy was necessary. Since then frequent treatments for exacerbations of sinusitis and otitis required medical attention.

Seven months ago the patient had nausea, vomiting, chills, and fever (104° F.) of unknown etiology, which disappeared after one week of treatment with sulfanilamide and iron capsules. Two months later she became pregnant (last menstrual period Oct. 7, 1937).

In the early weeks of pregnancy, large areas of ecchymosis on the upper chest and lower extremities appeared for the first time. Later smaller coalescent groups of similar character were observed on the arms. During the third month of pregnancy vaginal staining occurred for one day. The hemoglobin at this time (Tallqvist) was 70 per cent. The purpuric lesions persisted but there was no active bleeding. Medication did not include coal tar, gold, arsenical, benzol derivatives or other heavy metals; nor was x-ray or radium used. Iron supplemented by ABD vitamin capsules was the only therapy administered.

Physical Findings.—Marked pallor and weakness and purpuric skin manifestations, present in areas previously mentioned, characterized the general picture. A bilateral chronic otitis media was found; and through a large central left eardrum perforation a foul-smelling, thin discharge escaped. The mastoid scar was also noted. Nasal and gingival bleeding was active.

The abdomen, enlarged by a uterus reaching just above the umbilicus, indicated a six months' gravidity. Intrauterine activity and normal heart sounds attested fetal viability. The spleen was slightly enlarged.

The blood study (Dr. Nathan Rosenthal), which follows, confirmed the tentative clinical diagnosis of thrombocytopenic purpura with secondary anemia. Platelets 10,000; hemoglobin, 45 per cent; red blood cells, 2,790,000; white blood corpuscles, 12,000; polymorphonuclear leucocytes, 80 per cent, nonsegmented, 71 per cent, segmented, 9 per cent; eosinophiles, 2 per cent; basophiles, 1 per cent; lymphocytes, 9 per cent; monocytes, 8 per cent. Hematocrit, 21 per cent; reticulocytes, 2.5 per cent. Bleeding time: over 10 minutes; coagulation time, 13 minutes; tourniquet test, positive.

The cytologic study of the bone marrow aspiration was essentially normal except for a slight increase in megalokaryocytes. Cell count, 250,000; megakaryocytes, 13.2 per cent; myeloblasts, 1.4 per cent; myelocytes, 29.4 per cent; polymorphonuclear leucocytes, 48.8 per cent, nonsegmented, 28.6 per cent, segmented, 20.2 per cent; lymphocytes, 1.0 per cent.

Urine: Specific gravity 1.018; reaction, acid; albumin, faint trace; sugar, negative; 25 white blood cells and a few red blood cells per high power field; occasional clumps of epithelial cells.

Blood chemistry: Sugar, 100 mg. per cent; urea nitrogen, 8 mg. per cent; cholesterol, 275 mg. per cent; total protein 5.5 mg. per cent. Wassermann and Kahn tests, negative.

The patient received during the first week several blood transfusions (500 c.c. each), and the hemoglobin rose to 57 per cent. Daily increasing doses of moccasin snake venom were injected intracutaneously (0.1 c.c. to 0.4 c.c.).

General bleeding persisted, however; the spongy gum margins continued to ooze and began to manifest purulent changes. To interrupt the gravidity at this stage was considered inadvisable, since it interposed the hazard of hemorrhage and yielded no advantage. The patient's general condition did not improve.

Further temporizing was contraindicated and splenectomy was therefore immediately performed on March 21, 1938, by Dr. John Garlock, under avertin-ethylene anesthesia. Oozing from the pedicle and residual strands of adhesions necessitated drainage. Sutures were removed from the firmly healed subcostal wound on the ninth day.

The pathologic study of the spleen was reported by Dr. Paul Klemperer as follows: Weight 130 gm., size 15 by 8 by 4 cm. Hyperplastic pulp with many eosinophilic myelocytes; Malpighian corpuscles numerous and conspicuous.

Postoperatively, the patient gained strength quickly. The skin purpura disappeared gradually, and no new lesions were evident. Her blood count revealed striking improvement, showing a platelet increment from 10,000 to 220,000. Red blood cells, 3,600,000; white blood cells, 9,900; hemoglobin, 65 per cent; polymorphonuclear leucocytes, 82 per cent, segmented, 63 per cent, staff, 19 per cent; myelocytes, 1 per cent; lymphocytes, 14 per cent; monocytes, 3 per cent.

The brighter general appearance, the cessation of the vaginal, nasal, and gingival hemorrhage, and the improved postoperative picture indicated abatement of the disease.

On April 7, seventeen days after operation, without any apparent ill effects from the splenectomy, the patient was discharged. Her blood picture remained normal and fairly constant. Obstetric observations were within normal limits, the pelvis being ample upon both external and internal mensuration. Fetal heart was between 130 and 140.

The blood study on May 3, 1938, was as follows: Platelets, 147,000 (a few giant platelets); red blood cells, 3,690,000; hemoglobin, 66 per cent; white blood

cells, 14,000; polymorphonuclear leucocytes 73 per cent, staffs, 8 per cent; eosinophiles, 1 per cent; lymphocytes, 10 per cent; monocytes, 6 per cent; metamyelocytes, 2 per cent.

Two months prematurely uterine contractions spontaneously set in, and on May 12, at Beth Israel Hospital, after a ten-hour labor, the patient delivered normally. Although all necessary emergency measures were in readiness in anticipation of hemorrhage, they were not required since unexpectedly the blood loss incidental to delivery totalled only 30 c.c.

The post-partum course was uneventful. Involution of the uterus took place in the usual manner, and no further manifestations of the bleeding diathesis were observed. Daily post-partum blood counts were all normal.

Forty-three days after delivery the blood picture was still unchanged: Platelets, 180,000; red blood cells, 4,500,000; hemoglobin, 80 per cent; white blood cells, 9,600; polymorphonuclear leucocytes, 66 per cent; lymphocytes, 30 per cent; monocytes, 4 per cent.

The patient is completely well now (eight months post partum), and has been advised that no contraindications to a future pregnancy are believed to be present, since all blood studies during the period following delivery were normal.

As relates to the offspring of gravid patients with thrombocytopenic purpura, comparatively little is known. In fact, case reports are relatively few, testifying to the rarity of the condition.

Of poignant interest are the recent reports on the congenital aspects of this condition. Greenwald and Sherman,[11] in 1929, described an insufficiency of megalokaryocytes in the bone marrow of the offspring. The morphology of the maternal blood was not studied, however.

Sanford, Leslie and Crane,[29] in 1936, observed marked thrombocytopenia and increased disintegrative power of the platelets in both mother and newborn infant.

Davidson's[7] interesting paper, in 1937, describes a remission during a pregnancy eight and one-half years after splenectomy (epistaxis, skin purpura, platelets always between six and 47,000, and severe post-partum hemorrhage). The infant at birth had a severe hemorrhage and a low platelet count.

In our studies of the infant, totally different findings obtain. The clinical, blood and pathologic studies confirm conclusively the absence of purpura hemorrhagica. A complete description of the seven months' premature newborn infant, delivered fifty-three days following splenectomy of the mother, is presented.

The infant was a male, weighing three pounds, and living at birth. Its skin presented the characteristic dearth of subcutaneous fat as seen in prematurity, and was covered with normal colored vernix caseosa. There was no icterus of the skin or sclerae, and no cutaneous or mucosal purpura. The head showed no evidence of molding, no cephalohematomas were present. Respiration at birth was spontaneous, requiring no artificial means to initiate or maintain. The heart sounds were normal; rhythm regular, and rate normal. Breath sounds were heard throughout the pulmonary fields. The cry was feeble but not delayed. The abdomen showed no evidence of ascites, or masses. No congenital malformations of the mouth or palate were noted. The anus was perforate. Special incubator care was provided.

Blood count, on the first day of life, showed: Platelets, 170,000 (few giant platelets); red blood cells, 4,540,000; hemoglobin (Sahli), 122 per cent; color index, 1.3 per cent; white blood cells, 12,650; polymorphonuclear leucocytes, 68 per cent, staffs, 18 per cent, segmented, 50 per cent; lymphocytes, 23 per cent; monocytes, 8 per cent; myelocytes, 1 per cent; normoblasts, 7 per 100 white blood cells.

Ten cubic centimeters of blood was given intramuscularly, and during the first twenty-four hours the color remained good and the cry became stronger. Occasionally small amounts of breast milk regurgitated, but the next day feedings were well taken. The baby voided freely and passed meconium stools.

The blood count on the third day remained essentially as at birth, showing: Platelets, 167,000; red blood cells, 4,490,000; hemoglobin, 114 per cent; color index, 1.2; white blood cells, 11,900; polymorphonuclear leucocytes, 70 per cent, staffs, 9 per cent, segmented, 61 per cent; lymphocytes, 20 per cent; monocytes, 7 per

cent; eosinophiles, 2 per cent; myelocytes, 1 per cent; reticulocytes, 6.9 per cent; (normoblasts 10 per high powered field); bleeding time, 3½ minutes; coagulation time, 4½ minutes.

The slight edema of the pubic region, pelvis, and lower extremities which appeared on the second day was accounted for by posture (Fowler's position), rather than on the basis of a blood dyscrasia, since there was no jaundice or anemia, and also since the erythroblastemia disappeared before the seventh day of life. Six days after birth cyanotic spells appeared after feeding, and on the following day O_2 and CO_2 therapy was required. The baby took its feeding poorly, or not at all, and the temperature began to rise. Signs of atelectasis were discernible in the chest, and the day following (May 20) the infant was constantly and deeply cyanosed, notwithstanding continuous oxygen administration. Feeding was stopped and elysis substituted. The respirations that day became irregular, and at both bases of the lungs posteriorly, breath sounds could not be elicited. On the evening of May 20, eight days after birth, the baby died.

On post mortem examination (Dr. Freund), in addition to the usual anatomic evidence of prematurity (sparse subcutaneous fat, etc.), both lungs were found to be noncrepitant throughout and sank immediately when placed in water; the cut surface showed characteristic appearance of collapse. It is of interest that anatomically the spleen was entirely normal, as were the bone marrow, liver, etc. There was a small area of hemorrhage in the right apical visceral pleura of the lung and small mucosal hemorrhages in the jejunum, ileum, and bladder mucosa, all of which were interpreted as agonal.

CONCLUSIONS

1. An obstetric problem, in which a gravidity was complicated by purpura hemorrhagica, is presented.

2. Following splenectomy, the maternal blood morphology became normal, remaining so throughout the entire period of gravidity, as well as after delivery.

3. Of great importance is the fact, that the blood picture of the newborn also was entirely normal. In addition, post mortem examination (death due to pulmonary atelectasis) revealed no pathologic disturbances of the hematopoietic system.

4. We conclude that a newborn infant will be free of this disease, if delivered of a purpuric mother, if her blood picture, following splenectomy, reveals complete remission.

5. Contrariwise, however, the literature establishes that the disease is congenital when, despite splenectomy, the hematologic characteristics of purpura are found in the blood of the mother.

6. Furthermore, the question presents itself as to the role splenectomy played in the premature onset of labor (endocrine imbalance).

7. In addition, since there was essentially no blood loss at delivery, the thought arises as to the effect of splenectomy on post-partum hemorrhage.

8. The role of the spleen in the gravid patient remains to be determined. Such cases as above described, present opportunity for this study. Comparative observation of pregnancy in patients with and without their spleen may reveal its mechanism in pregnancy.

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PAPILLARY CYSTADENOCARCINOMA OF OVARY WITH HYDROTHORAX

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A CAREFUL search of the literature of the last twenty-five years has failed to disclose a single case similar to the one to be presented in this article. However, in 1937, Meigs and Cass[1] reported a series of seven cases of ovarian fibroma with ascites and hydrothorax, in which after removal of the tumor, the hydrothorax disappeared and the patient recovered.

Another article on the same subject was published[2] in November, 1937, by Rhoads and Terrell, who pointed out that because of the association of a pelvic tumor, apparently ovarian, with ascites and hydrothorax, a diagnosis of pelvic malignancy with chest metastases was made in several of these cases, as a result of which they were considered hopeless and operation was long deferred. Occasionally it may be impossible, Rhoads and Terrell state, even after partial aspiration, to exclude the presence of pulmonary metatases by x-ray, therefore they feel that an abdominal exploration in this type of case is justified and promises hope in a considerable number of cases in which the prognosis was previously regarded as hopeless.

Mrs. A. S., aged 50 (204382), was admitted to the service of Dr. B. M. Eis, on Aug. 9, 1937, complaining of heartburn and diarrhea. Family history irrelevant. Patient has been married 19 years, has one child 17 years old, has never been sick before. Menopause three years ago. For the last two months she has been complaining of heartburn, with gradually increasing dull epigastric pain until four days before admission, when a profuse, watery diarrhea began, persisting until admission. No other symptoms. On admission she had a temperature of 100.6° F., pulse 124, respirations 24, blood pressure 118/78. Flatness and markedly diminished breath sounds lower half of right chest. Heart normal. Abdomen: Fluid wave and shifting dullness. Mass felt in right lower quadrant arising from pelvis extending to level of umbilicus. Vaginal examination confirms impression that mass arises from pelvis. *Diagnosis:* Papillary cystadenocarcinoma of ovary with pulmonary metastases.

Physical findings: Kline test negative. Sedimentation: 62 mm. per hour. Blood count: Hg 62 per cent, white blood cells 7,850, polymorphonuclears 82 per cent, R.B.C., 3,050,000. Urine, acid; specific gravity 1.015; albumin, negative; sugar, negative; epithelial cells. Stool negative for occult blood. X-ray of chest: A homogeneous opacity involving the right chest indicating massive effusion.

Course.—Right chest aspirated, 2,000 c.c. serosanguinous fluid removed. Smear, no organisms. Culture sterile. Revolta positive. Guinea pig inoculated and on autopsy revealed no evidence of tuberculosis. Chest fluid smear: fibrin, many red blood cells, lymphocytes, monocytes and few polymorphonuclear cells. Occasional epithelial cell. No neoplastic cells noted.

X-rays of pelvis, skull, ribs, femoral necks, and of gastrointestinal tract including a barium enema showed no radiographic evidence of metastasis.

X-ray of chest after removal of 2,000 c.c. of fluid revealed two dense areas of opacity in the base of the right lung which were suggestive of the presence of metastatic malignancy. The presence of localized collections of residual fluid must also be considered.

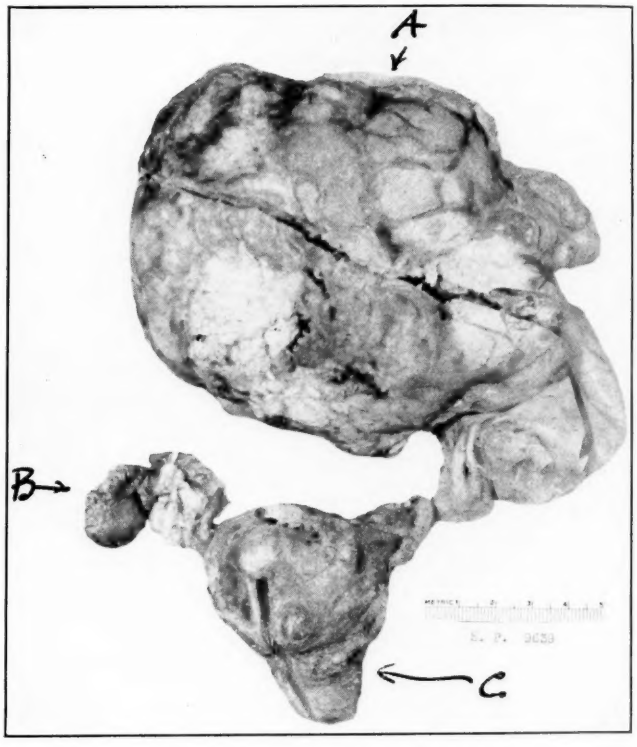

Fig. 1.—*A*, Tumor of left ovary; *B*, right tube and ovary; *C*, uterus.

Examination a few days later showed evidence of free fluid. Mass felt to right of midline coming up out of the pelvis extending to level of umbilicus, mobility restricted, not tender. On examination, uterus could not be differentiated from a large, hard, irregular nodular mass about the size of a five months' pregnancy. Mobility restricted but condition was not a frozen pelvis. Impression: Papillary cystadenocarcinoma of ovary. Laparotomy advised.

Operation: Anesthesia, nitrous oxide and ether. Midline lower abdominal incision. Large solid tumor mass with many papillary and cystic excrescences occupying the entire lower abdomen extending to level of umbilicus adherent to small intestines and omentum. All adhesions freed by blunt dissection and mass mobilized, when it was found to arise from the left ovary. On careful exploration no masses were found on the liver, omentum, intestines, or parietal peritoneum. The right tube and ovary were normal. Several small subperitoneal myomas on uterus. Mass extended posteriorly in back of the left broad ligament down to the level of the cervico-

uterine junction. A total hysterectomy and bilateral salpingo-oophorectomy were performed in the usual manner, raw surfaces peritonized with bladder reflection. Wound closed in layers without drainage (Fig. 1).

Histologic Report: Sheets of large polyhedral and cylindrical cells varying greatly in size, shape, and chromatin content of their nuclei, a number seen in a state of mitotic division. In places they tended to form acinar structures or appeared to be mounted on connective tissue stalks. Areas of necrosis were seen in places. The stroma was in places abundant, hyalinized, infiltrated with small round cells, large mononuclear cells and some polymorphonuclear leucocytes.

Diagnosis: Papillary cystadenocarcinoma of left ovary.

Postoperative Course: Patient ran a temperature from 100 to 102°, and on August 29 vaginal examination disclosed a bulging in the posterior cul-de-sac. The index finger was pushed through the vaginal vault and about 4 ounces of pus were evacuated. There was also a purulent discharge from the lower angle of the wound. Temperature thereafter remained normal.

X-ray of skull failed to reveal any evidence of metastasis. X-ray of chest revealed considerable improvement in the pathologic process, with evidence of residual thickened pleura at the right base. A diagnosis of metastatic disease of the ribs or lungs was not warranted from this study. Patient was discharged from the hospital on September 16. General condition good. Abdominal wound clean, granulating. Postoperative deep x-ray therapy given, a set of 20 high voltage treatments, abdomen and pelvis, 4,000 rat units. Patient has felt well since operation and examination on Jan. 17, 1938, showed a completely free, negative pelvis: wound firm, no free fluid, no masses, no tender areas. Chest negative. X-ray of the chest on January 13 showed no mediastinal, pulmonary or pleural pathology.

DISCUSSION

A point of unusual interest in this case is the x-ray picture after chest aspiration in which two shadows appear, described by the roentgenologist as either metastases or residual fluid. These shadows disappeared on the plate taken before the patient left the hospital, a period of only two weeks. If we accept the postulate that these shadows were metastases, it follows that they disappeared two weeks after removal of the primary tumor. This, however, occurs in the milder types of early malignant change, whereas in the case presented, the malignancy seems to be moderately advanced. Even the *possibility* of disappearance of metastatic foci in a case of this type emphasizes the importance of early operation. In view of the fact that roentgenologically the two chest shadows appearing after removal of the fluid were considered as either metastatic or residual fluid, the latter interpretation would tend to classify this case as belonging to the group reported by Meigs of ovarian fibroma with hydrothorax, the difference being that this patient had an ovarian cystadenocarcinoma instead of a fibroma. Meigs offers no explanation of the etiology of the hydrothorax in his cases. If we were to venture a physiologic hypothesis in explaining the coexistence of hydrothorax with ovarian tumors, we might consider the following:

It appears physiologically sound to state that more than one single factor is involved. Experimental work on animals, as described by Wiggers[4] in the reproduction of anasarca, indicates that the order of appearance is as follows: (1) elevation of venous pressure; (2) ascites; (3) hydrothorax; (4) subcutaneous and pulmonary edema. Edema is considered by some to be a compensatory mechanism through which an attempt is made to restore blood and fluids surrounding vital organs to a normal state. Aldrich[5] suggests that it may be protective, e.g., by diluting toxin. Wiggers tells us that forces and interactions in the production of edema are so many and variable that we must regard it as a chain of events in which an initial change leads to a series of subsequent alterations. In such a study, the serous cavities, it must be remembered, are considered part of the lymph drainage and productive system.

The initial factor in our case is the presence of a large pelvic tumor. This then presents the possibility of contributing to the chain of events by compression of

the large abdominal lymphatic channels, and so retarding return of lymph through normal channels. We know that capillary permeability is affected by histamine and similar substances produced by tissue injury and degeneration, consequently it is a factor in the formation of lymphedema in a case such as ours, in which toxic substances formed in degenerated tumor tissue are being constantly absorbed. The possibility of capillary endothelial damage caused by anaphylactic reaction to degenerated tissue products must also be considered here. It is not inconceivable that the liver, in attempting to eliminate an excess of toxins, puts out an increased amount of lymph. The liver itself does not grossly become edematous because of its very liberal lymphatic drainage. Filtration, however, with respect to the primary capillaries at the other end of the portal system, is different. When the filtration pressure exceeds the oncotic pressure, plus endothelial damage, the division line between capillary filtration and reabsorption is shifted to the venous side, thereby resulting in increased venous pressure. Lymph so formed may be absorbed to some extent by the chyle vessels and be returned to lymphatic circulation with liver lymph. The greater quantity, however, is eliminated into the peritoneal and pleural cavities by the large serous surfaces of the viscera, omentum, peritoneal and pleural coats. Under normal conditions a balance of forces in serous cavities is essentially absorptive. Fluids and even particulate matter introduced are absorbed, the former by blood capillaries, the latter by lymph channels (Cunningham[6]). When the avenues of escape through blood capillaries and lymph channels are abrogated, as by toxic damage to endothelium, increased permeability based on anaphylaxis, obstruction to lymph, fluid becomes trapped in large serous cavities and a vicious cycle results in ascites, pleural effusion and, if allowed to go on, subcutaneous edema. The above possibilities, it is true, are speculative, but, we feel, present a physiologic explanation of the edema.

SUMMARY

A case of papillary cystadenocarcinoma of the ovary with hydrothorax is presented in which the effusion disappeared after removal of the tumor. It should be emphasized that a patient with an ovarian tumor and hydrothorax is entitled to abdominal exploration even though malignancy is suspected. The condition may be a benign ovarian fibroma, in which case the patient is cured; but even though the tumor be malignant, early removal may be followed by disappearance of the fluid and in some cases even by disappearance of metastases. This case is presented with a plea to the internist for thorough pelvic examination in every case of hydrothorax, and for operation whenever a pelvic tumor is found, even though malignancy is suspected.

We acknowledge with thanks the assistance of Dr. Victor Woronov in the preparation of this paper.

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PRIMARY ADENOCARCINOMA OF THE VAGINA

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CARCINOMA of the vagina is uncommon. Most of those cases which occur are secondary to carcinoma elsewhere, usually higher in the genital or in the urinary tract. Of the small remaining group, the primary vaginal carcinomas, epitheliomas comprise by far the greater part; the rarest of all types is the primary adenocarcinoma.

The following case is one in which the diagnosis has been established microscopically, and the possibility of a primary growth from which the lesions might have metastasized appears to have been eliminated.

The patient is a white, 28-year-old, nulliparous female with this history: There had been a constant vaginal discharge from seven to eight years. This was usually worse after menstruation. In addition to the discharge, there was local irritation described by the patient as tingling and "sticking." During the past three years spotty bleeding had occurred at times, usually accompanied by an increase in the amount of discharge and the local irritation. Except for occasional mild dysmenorrhea, menstruation seemed normal. There was no history suggestive of pelvic inflammation or cystitis. A wide variety of treatment had been employed. Symptoms were almost invariably exaggerated. There were two exceptions to this: administration of estrogenic hormone and cervical cauterization to relieve a low-grade endocervicitis, were followed by some reduction in discharge and soreness. There were apparently spontaneous exacerbations and remissions at various times when the patient was under no treatment.

The patient presented a normal general appearance, temperature 98° F., pulse 72, blood pressure 116/76, height 65 inches, weight 125 pounds. Pupils round and equal reacting normally to light and accommodation. No exophthalmos or other apparent abnormality of the eyes. Teeth in good condition. Tongue clean and moist. Tonsils cleanly removed. No evidence of deformity, inflammation or other abnormality in the ears, nose, or throat. No cervical adenopathy. Thyroid not palpable and showing no evident enlargement. Tendon jerks present and normally active. No abnormal reflexes and a negative Romberg.

Chest showed good and equal expansion with normal breath sounds and resonance throughout. The heart sounds were regular and of normal quality; no evidence of cardiac enlargement. Fluoroscopy and flat films of the chest were negative. The breasts were well-developed, symmetrical, and were free from masses or tenderness.

The abdomen was nearly flat and without scars. There were no palpable masses; the liver was not palpable and was not percussibly enlarged. Kidneys and spleen were not palpable. No tenderness anywhere in the abdomen. No visible or palpable adenopathy in the inguinal regions.

The perineum presented the normal nulliparous appearance. There was no evidence of old or recent inflammation of the urethra, Cowper's or Bartholin's glands.

The cervix lay somewhat to the right of the midline. It had a normal appearance.

On examination of the vagina there were multiple, flat, hyperemic lesions varying in size from 0.1 cm. to 0.5 cm. in diameter. These were distributed throughout the entire vagina but were more numerous in the lower third.

On bimanual examination the uterus, including the slightly deviated cervix, was found movable, normal in size, shape, and position except as stated. There was no palpable pathology in the adnexa.

Urinalysis of a catheterized specimen showed no pus, blood, albumin, or sugar. Blood Kolmer and Kline were negative. Smears were negative for gram-negative diplococci and a saline suspension of the vaginal secretion showed no *Trichomonas vaginalis.*

Biopsy specimens from several lesions were examined by Dr. A. C. Broders and diagnosed papillary adenocarcinoma Grade 1. On subsequent diagnostic curettement of the uterus no evidence of malignancy was found.

Five cases of primary adenocarcinoma of the vagina have been reported in the literature. Strachan described two cases, which represented an incidence of 0.55 per cent in 328 cases of gynecologic carcinoma. This is greater than in most similar series of cases. He likewise gives the incidence for all types of primary vaginal carcinoma as 3.9 per cent which is also relatively high.

Moench found two cases of primary adenocarcinoma in 59 primary vaginal malignancies in the Mayo Clinic material up to 1931. She states that one epithelioma of the vagina was found for every 43 epitheliomas of the cervix between the years 1915 and 1925.

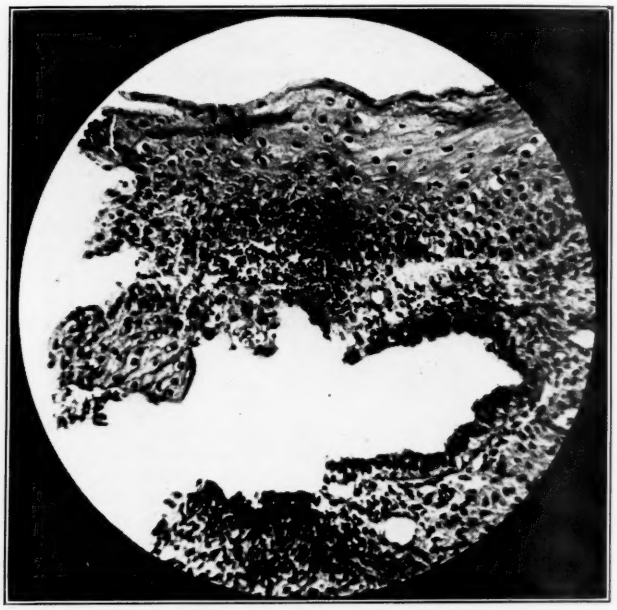

Fig. 1.—Section of a gland of the Grade 1 adenocarcinoma situated beneath the squamous mucous membrane. This carcinoma is comparable in malignancy to the so-called malignant adenoma which not infrequently occurs in the large intestine.

Strachan quotes Gurlt who found 0.19 per cent of primary epitheliomas of the vagina in 59,600 collected cases. Other incidences of primary malignancies of the vagina, quoted by this author, ranged from 0.06 to 0.43 per cent. Strachan further states, "The percentage incidence of primary adenocarcinoma is therefore infinitesimal in any large series of gynecologic cancer, so that individual cases when they occur are usually reported."

Williams found only two undoubted cases of primary vaginal carcinoma in the records of the Pathological Department of Boston Hospital in twenty-five years. Neither was adenocarcinoma. With Moench's observation of only two instances of primary adenocarcinoma in 59 cases of primary carcinoma of the vagina, it is apparent that the incidence of primary adenocarcinoma of the vagina must be small indeed.

Emmert found 30 cases of primary carcinoma of the vagina in 1,546 cases of genital cancer in Barnard Free Skin and Cancer Hospital, St. Louis; none was adenocarcinoma. His study included seven additional cases from private practices. Of these, one case from Dr. Gellhorn's practice, a 27-year-old woman, was adenocarcinoma. There is no further description of this case.

A review of the cases previously presented suggests that suspicion of primary vaginal adenocarcinoma might be occasioned only by the presence of one or more vaginal growths of considerable size. Such an appearance did not characterize the case presented. In this instance the gross appearance varied widely from the lesions previously described.

Our experience with this case would suggest that malignancy must be considered a possibility in any surface lesion of the vagina which is resistant to treatment.

Study of the group of cases makes it apparent that age is not an invariable factor and that pregnancy has nothing to do with the occurrence of this lesion.

Differential Diagnosis.—Differentiation of primary from secondary carcinoma presents some difficulty. Particularly the possibility of a primary lesion higher in the genital tract or urinary tract must be eliminated. Taussig has reported a case of hypernephroma in which the metastasis occurred near the external urethral opening. In addition to several other diagnostic points it was stated in this report that, "A primary malignancy at this point (periurethral area) has practically never been observed." It is significant that in the case here presented a number of the lesions occurred within 2 to 3 cm. of the urethral opening.

Treatment.—Treatment in the cases previously reported has consisted of some surgical procedure combined with application of radium, or radium treatment alone. Surgery alone is regarded quite pessimistically by some authorities. The incidence of primary adenocarcinoma is too small to justify conclusions as to the most effective treatment. Electrocoagulation was employed in the present case, but too recently to make its effectiveness evident. Guarded prognosis appears to be eminently justifiable.

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Heuck and Hauser: Thirteen Cases of Malignant Chorionepithelioma, Ztschr. f. Gynäk. **117:** 1, 1938.

A series of 13 cases of malignant chorionepitheliomas is reported. Five cases followed full-term labor or abortion, seven occurred after hydatid mole and one followed a tubal pregnancy. Cures were obtained in 50 per cent of the cases. The Aschheim-Zondek reaction proved of the utmost importance not only diagnostically but also to determine the results of treatment. Lutein cysts were found only in cases of hydatid mole (in 5 out of the 7 cases). If after removal of an hydatid mole, lutein cysts appear, it is a highly suspicious indication of chorionepithelioma but not absolute proof.

It is not possible to determine whether or not a chorionepithelioma is present from the microscopic examination of an hydatid mole; an Aschheim-Zondek test is most helpful.

Metastases were observed in six of the 13 cases and in five led to death.

J. P. Greenhill.

POSTENCEPHALITIC PARKINSONISM COMPLICATED BY PREGNANCY

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THE occurrence of pregnancy in patients with postencephalitic Parkinsonism is, according to some observers, a serious or even fatal complication. Roques[1] made a very extensive study, reviewed the literature up to 1928, and added a number of new cases. He concluded that pregnancy occurring during the acute stages of encephalitis apparently increases the chances of a resulting Parkinsonism and that in subsequent pregnancies this postencephalitic sequel becomes aggravated. Bland and Goldstein[2] hold the same ideas from their review of the literature and feel justified in concluding that this combination of conditions is not a happy one, the case they reported terminating fatally on the eighth day following delivery. Critchley,[3] who reported 7 cases, felt that pregnancy is not aggravating to Parkinsonism.

Roques reported 40 cases, Bland and Goldstein 1, Critchley 7, Tranquilli-Leali[4] 1, Voron, Pigeaud and Nova[5] 1, Ottow[6] 1, Achard[7] 4, De Rezende[8] 1, Thwaites Lastra, Bizzozero and Alegre[9] 1, and Hernández Ramirez[10] 1. We add to these, 2 patients with 3 pregnancies who have come under our observation at the Presbyterian Hospital.

Case 1.—Mrs. E. Z. R., aged 20, was born in the United States. This patient was first seen in our out-patient obstetrical clinic on June 29, 1936. She had been amenorrheic since April 23, 1936. Her past history revealed that she had had diphtheria, and at the age of 10 she had fallen from a second floor porch. The tremors of the body were dated from the time of the fall. Menses began at 11, and had been recurring at regular (twenty-eight to thirty days) intervals, lasting three to four days with moderate flow. The patient had no history of infantile spasticity or rickets, having learned to walk at one year of age. She was 4 feet 11 inches tall and weighed 108 pounds. General physical examination was negative. Blood pressure was 110/80, hemoglobin 80 per cent, Wassermann reaction negative, vaginal smears negative, and urine normal. Pelvic measurements were within normal limits. Bimanual palpation revealed the presence of an early pregnancy. Because of the coarse generalized tremors, the patient was referred to the neurologic clinic.

Neurologic examination (Dr. J. Favill), July 1, 1936: No changes in the cranial nerves, coarse tremor of the tongue, and pupils that reacted normally to accommodation and light. There was a marked spasticity of both sides of the body, being more exaggerated on the left. There was little control of the left arm, the patient frequently calling the right into use to help the left carry out movements. The reflexes were all present but were slightly decreased on the left side. The speech was slow and tremulous with some slurring. The patient stated that the tremor was greatly exaggerated in the presence of strangers. A diagnosis of postencephalitic Parkinsonism was made, and a favorable prognosis given. Hyoscine hydrobromide, gr. 1/100 twice daily, was prescribed. This was changed to tincture stramonium, 30 drops three times daily, when it was found that the patient could not swallow tablets.

Combined neurologic and obstetric observation found the patient approaching term in an unchanged condition. She entered the hospital in labor at 1:00 P.M. on Jan. 1, 1937, having good contractions at three- to five-minute intervals. At 2:15 P.M. 4½ gr. of pentobarbital sodium and 1/200 gr. of hyoscine hydrobromide were administered and at 2:45 P.M. another 1½ gr. of pentobarbital were added. The patient was restless but cooperated well throughout labor. Dilatation proceeded, and

at 4:50 P.M. the membranes were artificially ruptured. At 6:10 P.M. ethylene-oxygen analgesia was started and at 6:38 P.M., after episiotomy, the patient delivered a 6 pound 5½ ounce female child. The baby was somewhat apneic but was readily resuscitated by the use of tracheal catheter and hot and cold water baths. The placenta was expressed at 6:45 P.M. The episiotomy was repaired with the patient under gas anesthesia.

The patient was returned to the ward where she was found to be very restless and tossed about considerably, having several attacks of vomiting. The restlessness did not subside and became so pronounced that at 12:10 A.M. it was necessary to administer sedation in the form of a retention enema of sodium bromide and chloral hydrate. Following this she had an uneventful puerperium, nursed her baby, and left the hospital on the tenth post-partum day.

On follow-up examination in the neurologic clinic, July 21, 1937, the patient was found to be in an unchanged condition, the pregnancy having had no demonstrable effect upon the Parkinsonism.

The patient again appeared in the prenatal clinic on July 1, 1938 with the history of having had her last menstrual period on Jan. 24, 1938. During the first two months of this pregnancy there had been some nausea and vomiting, but since that time she had been well. She was found to be about six months pregnant, weighed 121¼ pounds, had a blood pressure of 122/68, a negative Wassermann, a hemoglobin of 80 per cent and a normal urine. The neurologic condition was the same as on discharge with the last pregnancy. The patient was followed to term with the only recommendation being that she have a hospital delivery. She was admitted to the hospital on Oct. 30, 1938 in labor. Labor began at 6:00 A.M. At 9:40 A.M. the membranes ruptured spontaneously and she delivered normally at 9:50 A.M. after episiotomy. The episiotomy was repaired very rapidly (ten minutes) under very light gas anesthesia. Neurologic examination during the puerperal period (Dr. L. Avery) revealed no change from the previous condition and elicited no special precautions as to nursing the baby or subsequent pregnancies.

CASE 2.—Mrs. P. H., aged 23, was born in the United States. She appeared in the out-patient department prenatal clinic as a primagravida, her last menstrual period having been on May 15, 1937, and her first examination took place on Jan. 10. 1938. She had been born at full term, developed normally and graduated from grade school at 14. The past history revealed an attack of influenza in childhood and a fall when 5 years of age. Following this fall she developed a tremor of the right side of the body and head. Menses began at 13, came irregularly at two- to three-month intervals, lasted four to five days and the flow was moderate. Physical examination revealed no abnormalities except as recorded in the neurologic clinic. The patient was 5 feet 2 inches tall and weighed 139¾ pounds. Laboratory tests revealed negative Wassermann reaction and vaginal smears, blood pressure 120/80, hemoglobin 80 per cent, and urine normal.

Neurologic examination (Dr. W. Haines), Jan. 10, 1938: "History of tremors since a fall at 5 years of age. Tremors more marked on right side, and can be controlled to some extent by effort on the part of the patient. No changes in the special senses. No changes in the cranial nerves, normal sensation, poor coordination, tremors of extremities and head more marked on the right side with the right hand held in a clawlike spastic manner and the head tremor resembling a torticollis." A diagnosis of postencephalitic Parkinsonism was made. No specific treatment was recommended except that hospital delivery was advised and prolonged inhalation anesthesia, especially with ether, was cautioned against.

The patient went into labor at 9:00 P.M. on Feb. 16, 1938 and entered the hospital at 1:00 A.M. on Feb. 17. Labor progressed satisfactorily and the patient delivered spontaneously, without episiotomy, at 4:36 A.M. The placenta was expressed at 4:41 A.M. The patient had a small amount of ethylene-oxygen analgesia, with no true anesthesia. She reacted in all ways as does the normal patient. The baby weighed 7 pounds 5 ounces, cried spontaneously and was normal in all respects. The puerperium was uneventful except for a slight temperature rise on the third and fourth postpartum days ascribed to subinvolution. Following the use of fluid extract of ergot, the uterus descended and the puerperium progressed without further in-

cident. The patient nursed her baby and left the hospital on the tenth postpartum day. Follow-up neurologic examination revealed no change in the patient's condition.

DISCUSSION

The apparently harmless effect of the pregnancies upon the Parkinsonism in these two patients leads us to feel that the authors who took such a serious view of the association of these conditions have been unduly alarming. This difference in opinion may be explained when we state that most of Roques' patients became pregnant soon after their attacks of acute epidemic encephalitis and the patient reported by Bland and Goldstein had the onset of her Parkinsonism three years before her pregnancy. The disease of the patients here reported was of long standing, 10 and 18 years, respectively. Roques states that pregnancy is contraindicated in patients with postencephalitic Parkinsonism until at least four years have elapsed since the disease has become stationary. In recent cases he advises therapeutic abortion, and in all instances he stresses very close observation with termination of the pregnancy as soon as there are any signs of progress in the neurologic condition regardless of the stage of gestation. This appears to be sound advice but, as Roques himself says, he may have a rather distorted view of the situation because the cases he reviewed from the literature and those of his own were all patients in whom the acute encephalitis was fairly recent or in whom the Parkinsonism was aggravated by the pregnancy. On the other hand there may have been any number of patients with Parkinson's disease who may have weathered pregnancy, labor, the puerperium and the lactation period uneventfully, and were therefore considered not worthy of report.

According to other authors, the danger periods in pregnancy for these patients are the early months with the necessary bodily readjustments, the labor with its attendant stress and strain, the puerperium with the changes meant to bring the organism back toward a normal state and the lactation period with the constant strain upon the maternal mechanism.

In all reports studied the pregnancy and labor were not found to have been affected by the Parkinsonism, most authors feeling that labor is facilitated because the pain threshold in these patients is raised and the mental acumen lowered. Lower limb spasticity may present a difficulty in making the use of the lithotomy position rather impossible. Roques favors a short second stage with delivery as soon as conditions are favorable for low forceps application. All authors agree that the presence of Parkinsonism does not influence the incidence of sterility, abortion, or pregnancy toxemia.

After observing these two patients we feel that chronic postencephalitic Parkinsonism is no contraindication to pregnancy, and that the neurologic condition is not adversely affected by the pregnancy, puerperium, lactation, or even the labor, providing prolonged inhalation anesthesia is not employed. Under the combined care of the obstetrician and neurologist, and with proper mild sedation throughout the pregnancy, it is felt that the patient with chronic Parkinsonism is no worse an obstetric risk than is the normal woman. The only factor that may lead to restriction of activity for such patients is the individual ability to maintain equilibrial stability in the face of the increased weight and unwieldy abdominal protruberance occurring late in pregnancy. As one of our neurologic consultants put it, "the economic situation of the patient should be the guide as to the number of pregnancies she may have, and on this basis alone should sterilization become a consideration."

The only precaution that we advocate in these patients is one relating to anesthesia. All general inhalation anesthesia produces some cerebral edema. The addition of such edema to a brain which has already been insulted may prove to be annoying or even dangerous. This is clearly demonstrated in our two patients. Patient 1, in her first labor, had prolonged ethylene-oxygen analgesia and deep anesthesia for the episiotomy repair. She exhibited an unusual amount of post-delivery vomiting and restlessness in spite of adequate prepartum sedation. This was not seen after her second labor or in Patient 2 where no truly deep anesthesia was used. Because of this, we believe that in patients having postencephalitic Parkinsonism who come to the delivery table, an effort should be made to use anesthesia other than of the inhalation types. If these are not available, a minimum of inhalation anesthesia or better yet analgesia should be administered by an expert anesthetist.

CONCLUSIONS

1. Chronic postencephalitic Parkinsonism is not a contraindication to pregnancy.
2. Mild sedation throughout pregnancy is advised.
3. These patients may nurse their babies.
4. Pregnancy, labor, and the puerperium are not affected by the presence of the Parkinson syndrome.
5. Precaution must be taken in using prolonged inhalation anesthesia on patients with Parkinsonism.

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REPORT OF TWO CASES OF TWINNING IN ECTOPIC PREGNANCY

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AREY,[1-3] in 1923, discussed the embryology of unilateral twin ectopic pregnancies and reviewed all reported cases. He found what he considered 40 authentic, 8 questionable, and 4 doubtful presentations in the literature.

Falk and Blinick,[5] in November, 1937, recorded two cases of their own that occurred in Harlem Hospital in New York and reviewed all the additional cases on record since 1923. They accepted, as authentic, 65 cases. I have been unable to find any recorded cases since November, 1937. Two additional cases of unilateral twin ectopic pregnancies are now presented, both of which occurred in Mount Sinai Hospital, Philadelphia, within a period of five weeks.

Case 1.—A. S. (No. 8506), aged 36 years, first entered the hospital July 25, 1938, with chief complaints of pain in the lower left quadrant, chills, and fever. The patient was a para v, gravida v, her last delivery occurring eight years ago. For the past five years the patient had not been living with her husband. Her menses were always normal. The last menstrual period was July 18.

Physical examination revealed an obese, pallid white female about 38 years of age who complained of weakness but did not appear to be in acute distress. Her temperature was 101.8° F.; pulse, 94; respiration, 30; blood pressure 120/70. A slightly tender mass was palpated in the left lower quadrant that seemed to arise from the pelvis and extend up to the umbilicus. Because of the unusual obesity, the pelvic examination was unsatisfactory. The cervix appeared normal. A normocytic anemia associated with leucocytosis was present: Hb, 62 per cent; red blood count, 3,140,000; white blood count, 19,000; polymorphonuclears, 83 per cent.

It was thought that the patient had a degenerating fibroma of the uterus. Medical consultants advised against a laparotomy. With conservative treatment the temperature dropped to normal in two days and the patient was discharged on August 10, with instructions to report later for operation.

Three months later, on Oct. 31, 1938, the patient was again admitted with vaginal bleeding and knifelike pain in the left lower quadrant, dating since Oct. 21, 1938.

The patient had had amenorrhea associated with intermittent vaginal bleeding and occasional pain since her discharge from the hospital. The bleeding and pain had become more severe on October 21 and had persisted until she entered the hospital. The patient appeared markedly pale, weak, and complained of sharp lower abdominal pain. Again the chief finding on physical examination was a tender football-size mass filling the left lower abdomen and seemingly springing from the left side of the pelvis. The mass was distinctly more tender on this admission. The temperature was 102° F.; pulse, 105; respiration, 26; blood pressure 136/70. The admission blood count again revealed a normocytic anemia and leucocytosis: Hb, 50 per cent; red blood count, 2,620,000; white blood count, 37,600; polymorphonuclears, 94 per cent.

A blood transfusion was administered and an emergency laparotomy was performed on the evening of admission. A hemorrhagic foul-smelling, necrotic mass was found filling the left pelvis and extending into the left abdominal cavity, almost to the umbilicus. The right tube and ovary were normal; the uterine wall was intact. As the gangrenous mass was being removed, two small fetuses came into view. The left tube and ovary were not recognizable. The foul, hemorrhagic material was removed as completely as possible. A portion of the unorganized mass which was adherent to the mesentery of the sigmoid was not disturbed. The uterus was then removed. A drainage tube and gauze packing were inserted into the cul-de-sac.

The patient received four blood transfusions within ten days of operation, and responded excellently. Complete recovery was delayed by a subfascial collection of pus which was drained under anesthesia on Nov. 24, 1938. The patient was discharged in good condition on Dec. 11, 1938.

Excerpts from Pathologic Report: "Two small male fetuses measuring 4.5 and 4.0 cm. accompany the specimen" (an enlarged supravaginally amputated uterus).

"*Diagnosis:* (1) Twin ectopic pregnancy. (2) Suppurative perimetritis with diffuse myometritis."

Remarks: One cannot state absolutely whether this case of twin ectopic pregnancy was tubal or abdominal in origin. The fact that no left tube or ovary was seen macroscopically or microscopically seems to indicate that the pregnancy was primarily tubal and that stretching and inflammation of the tube caused localized vascular damage and gangrene with or without rupture. It is also impossible to state definitely whether the twins were monochorial or dichorial in origin since placental or chorionic tissue could not be found. The fetuses appeared to be about three or four months of age, more mature than the measurements indicated. They were well preserved and no abnormalities were evident.

CASE 2.—Y. B. (No. 9129), aged 28, a nullipara, entered the hospital with chief complaints of low cramplike abdominal pain and bleeding. She had been married eight years. Shortly after her marriage she was told by her family physician that she could not conceive because of a retroverted uterus. Menstruation had always been normal except for mild dysmenorrhea. Her last menstrual period was Sept. 20, 1938. On Nov. 19, 1938, the patient noticed vaginal bleeding. The bleeding was scanty and intermittent and her physician treated her for threatened abortion. On Dec. 1, 1938, the bleeding became more profuse and the patient felt severe knife-like pelvic pain. A consultant advised immediate hospitalization.

Physical examination revealed a young white female approximately 30 years of age, very pale and restless and in extreme distress from abdominal pain. The temperature was 100° F.; pulse, 110; respiration, 30; blood pressure, 120/70. The significant finding on physical examination was a rigid, tender abdomen. Pelvic examination revealed extreme tenderness in the right cul-de-sac with bulging.

The admission blood count showed a normocytic anemia with leucocytosis to be present: Hb, 56 per cent; red blood count, 2,700,000; white blood count, 18,000; polymorphonuclears, 80 per cent. The urinalysis was negative. A diagnosis of ectopic pregnancy was made.

On the evening of admission an emergency laparotomy was performed. The peritoneum was congested and purplish; free hemorrhagic fluid was present in the peritoneal cavity. The right tube was enlarged to the size of a large pear and ad-

herent to the sigmoid posteriorly. While the tube was being delivered it ruptured and two small fetuses dropped into the pelvis. The tube was removed and the peritoneum was closed without drainage.

The patient had an uneventful recovery and was discharged on Jan. 14, 1939, in good condition.

Excerpts from Pathologic Report: "There are two small male fetuses measuring 5 cm. in length. These are well preserved and show no abnormalities. *Microscopic Diagnosis:* Ruptured tuboovarian pregnancy (probably primarily tubal)."

Remarks.—Although the cord attachments of the fetuses could not be made out, the cavity from which the fetuses dropped was easily discernible in the removed specimen. The cavity was lined by a bluish membrane and in one area there was a rounded mass of chorionic tissue about 4 cm. in diameter. This case appears to be an example of monochorial tubal twin pregnancy.

SUMMARY

Two cases of unilateral twin ectopic pregnancy are presented, bringing the total number of reported cases to 67. That both cases should have occurred in one hospital in a period of five weeks is a rare and interesting medical coincidence.

I wish to take this opportunity to thank Dr. Charles Mazer and Dr. Charles Wachs for permitting me to report these cases.

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SEVERE MENORRHAGIA AS THE ONLY SYMPTOM OF ESSENTIAL THROMBOCYTOPENIC PURPURA CURED BY SPLENECTOMY*

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Dysfunctional uterine bleeding occurs quite frequently during puberty. It is often of such severity as to require heroic treatment, and occasionally terminates fatally. The cause of such bleeding is generally attributed to the same type of endocrine derangement responsible for the dysfunctional menometrorrhagia of mature women. However, the occasional occurrence of fatal uterine hemorrhage in the course of a blood dyscrasia, such as leucemia,[1] pernicious anemia,[2] or thrombocytopenic purpura,[3] makes a thorough search for obscure hematologic factors imperative in every instance of excessive uterine bleeding during puberty. The recognition of so singular a cause of uterine hemorrhage, even though seldom, may be life-saving by enabling the application of specific therapy.[4] The basic importance of this principle is illustrated by the following case history which describes the occurrence of almost mortal menorrhagia as the only symptom of essential thrombocytopenic purpura in a girl at puberty, and the curative effect of splenectomy.

A. F. (Mt. Sinai Hosp. Chart No. A5559), white female, aged 13, was admitted to the gynecologic ward, June 17, 1938, for the treatment of severe menorrhagia of three weeks' duration. This was her second menstruation. The first, which occurred six months earlier, on Dec. 20, 1937, was a moderate flow for fifteen days. Close questioning concerning her past medical history elicited the information that suturing was required to control an excessive gingival hemorrhage following extraction of a tooth at the age of 11 and that the slightest trauma usually produced noticeable ecchymoses. The patient's family and social histories were irrelevant.

*Presented at a meeting of the Obstetrical Society of Philadelphia, January 5, 1939.

On admission, the patient appeared to be an acutely ill, well-developed, pubescent girl. Her temperature was 100° F., and her pulse and respiratory rates were 120 and 20, respectively. The blood pressure was 96/52. General physical examination revealed marked pallor of the skin and mucous membranes, a hemic (functional) systolic murmur at the pulmonic area, a palpable spleen, a single ecchymosis on the anterior surface of the left thigh, and steady vaginal bleeding through a falciform hymen. Rectal examination of the pelvic organs revealed no abnormality. Jaundice, lymphadenopathy, and gingival hemorrhage were notably absent. Blood studies disclosed the presence of a severe normocytic anemia with 45 per cent of hemoglobin (Sahli), 2,350,000 erythrocytes, 18,700 leucocytes, and 7.2 per cent of reticulocytes. The fragility of the erythrocytes was normal. The bleeding and coagulation times were seven and four minutes, respectively, and the platelet count, 190,000. The blood sugar and urea nitrogen values were within normal limits, and the blood Wassermann reaction was negative. A specimen of urine obtained by catheterization showed no abnormal constituents. The basal metabolic rate was plus 7 per cent.

In the absence of laboratory findings pointing to the presence of a blood dyscrasia, a tentative diagnosis of dysfunctional uterine bleeding was made. The patient was given during the course of a week, in addition to a hypernutritious diet, three blood transfusions of 500 c.c. each, five daily intramuscular injections of anterior pituitary-like substance of 200 rat units each, and daily hypodermic injections of increasing doses of mocassin snake venom in 1:3,000 dilution. The initial dose of the latter was 0.4 c.c. and the maximum dose, reached in four days and maintained for three additional days, was 1.0 c.c. The uterine bleeding continued unabated, and the anemia persisted despite the multiple blood transfusions. Repeated blood studies showed a rising bleeding time (from seven to twelve minutes), a falling platelet count (from 190,000 to 100,000), and a total absence of clot retraction.

The presence of essential thrombocytopenic purpura was suspected in view of the altered hematologic findings. This diagnosis was further supported by the elimination of an organic uterine lesion through curettage (the endometrium was atrophic and dysplastic) and by the exclusion of defective hematopoiesis through study of aspirated, sternal bone marrow. On this basis, in addition to repeated blood transfusions, therapeutic agents of reputed value in essential thrombocytopenic purpura were tried, namely, large oral doses of cevitamic acid,[5] massive injections of calcium and parathormone,[6] and roentgen irradiation of the spleen.[7] A week of such intensive therapy was fruitless. On June 30, 1938, after fourteen days of hospitalization, the uterine bleeding was as severe as on admission and the patient's hemoglobin was 50 per cent (Sahli) despite the five transfusions. The splenic enlargement increased, and the hematologic picture of thrombocytopenic purpura became definite, namely, complete absence of clot retraction and reduction of the platelet count to 80,000. The failure of all modes of nonsurgical therapy, the continued uterine bleeding, and the presence of normal bone marrow seemed to warrant a splenectomy which was performed by Dr. B. Lipshutz on July 1, 1938. The operation was preceded and followed by blood transfusions. The patient suffered no unusual reaction.

The anticipated salutary effect of the splenectomy was prompt and dramatic. The previously refractory uterine bleeding ceased abruptly within twenty-four hours of the operation. The splenectomy wound healed by primary intention and the patient, afebrile and symptom-free, was discharged from the hospital on the tenth postoperative day. She menstruated normally five weeks after the splenectomy and at twenty-eight-day intervals to date. The patient has remained in good physical condition and gained 12 pounds during the past five months. On Dec. 20, 1938, her hemoglobin was 102 per cent (Sahli), the erythrocytes 5,270,000, and the platelet count 230,000.

COMMENT

Essential thrombocytopenic purpura may defy recognition when there is no numerical reduction of the circulating platelets. In such instances, study of the clot retraction and examination of the bone marrow may be valuable. The absence of clot retraction denotes a qualitative alteration of the platelets which renders them incapable of aiding clot formation. The absence from the bone marrow of megakaryo-

cytes, the progenitors of circulating platelets, is indicative of faulty platelet formation and also bespeaks the futility of splenectomy. On the other hand, the presence of megakaryocytes in the bone marrow suggests that the dyscrasia is not caused by defective hematopoiesis but rather by the probable elaboration of a platelet-destroying substance, thrombocytopen,[8] by the spleen, the removal of which may prove eminently beneficial. The curative effect of splenectomy in essential thrombocytopenic purpura may also be foretold, as suggested by Peck and his associates,[9] and as illustrated in this instance, by the refractoriness of the bleeding to the administration of moccasin snake venom.

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2116 SPRUCE STREET
1820 SPRUCE STREET

DISCUSSION

DR. GEORGE W. OUTERBRIDGE.—I have recently seen a remarkably similar case. This patient was also a white girl, 14 years of age. She was admitted to the Abington Hospital on the ninth of March, 1938, with a history of her first period having begun three weeks before, and having continued with profuse bleeding in spite of medication and injections by the family physician. Her history showed she had always developed purpuric areas following slight bruising, and since the onset of the bleeding she had developed several of these areas. She did not bleed excessively following cuts but in early childhood she would often awake with blood on her lips. The blood count showed 49 per cent hemoglobin, 1,900,000 red cells, and 7,600 white blood cells, 28,000 platelets, 6 per cent recticulocytes. The coagulation and bleeding times were each two minutes. Rectal examination was negative. She was given three transfusions, after which the bleeding stopped promptly. Nine days after admission her hemoglobin was 85 per cent and the red blood cells 4,200,000. She was discharged with instructions to her physician.

The patient was readmitted on May 3, after staying home for six weeks. She reported that she had remained free of bleeding for one month, except that on awakening she noticed blood on the lips and brushing of the teeth caused hemorrhage from the gums. Two weeks before readmission slight vaginal bleeding began and continued for ten days after which, during the five days prior to admission, it was profuse. The blood count showed hemoglobin 62 per cent with 3,000,000 red cells, but only 4,000 platelets. The platelet count was repeated a day or two later and 7,000 were found. A splenectomy was done on the 16th of May by Dr. Duncan B. Pfeiffer, following which the platelet counts were taken daily and rapidly increased, at one time reaching 500,000. She was discharged on June 22, 1938.

Her menstrual periods have been regular since her operation, of three days' duration, with no excessive bleeding and no discomfort. She has no bruising of the skin and no bleeding of the gums or lips. She is active in school and indulges in all the common activities of a girl of her age. She has gained 16 pounds since leaving the hospital.

PREGNANCY FOLLOWING MODIFIED ESTES OVARIAN TRANSPOSITION AND CUFF OPERATION ON OVIDUCT*

Visualization of End Results at the Time of Elective Section

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ESTES devised a procedure which provided for the conservation of the ovary in those cases which presented such extensive adnexal pathology that a complete hysterectomy ordinarily would have been indicated. This preservation of the ovary permits the continuance of the menstrual cycle, maintains normal hormonal balance and provides the possibility of pregnancy. The procedure first consisted of removing the diseased tubes, carefully preserving the ovarian circulation, resecting the ovaries and saving as much as possible of the healthy ovarian tissue. These resected ovaries were then transposed over the cornual area of the extirpated tubes. Pregnancy resulted in about 8 per cent of the cases. Estes later modified this procedure by making a stab wound through the interstitial portion of the uterus in order to keep patent an opening into the uterine cavity.

At Bellevue Hospital we have further modified this technique. We ream out the interstitial area of the uterus, thereby preserving a more or less permanent opening, and suture the resected ovary over this newly created ostium into the uterine cavity.

The following case report is presented for two reasons: First, pregnancy occurred after performing a modified Estes transposition of the ovary, and a cuff operation on the tube of the opposite side. Second, we were able to visualize the end results of the above operative procedure at the time of elective cesarean section.

Mrs. M. B., 28 years of age, married two years, was admitted to Bellevue Hospital on May 30, 1936. Her chief complaint was sterility. She had been endeavoring to become pregnant for two years without success. No contraceptives were ever used. Her husband was found to be virile. Menstruation was regular, of the 28-day type, duration five to seven days. Patient had dysmenorrhea throughout her period which was severe enough on the first day to compel her to stay in bed. At times it was necessary for her to remain in bed throughout her entire period. There was no leucorrhea. She complained of slight dyspareunia.

The general health of the patient was good. Physical examination was essentially negative. Pelvic examination revealed cervix clean, smooth and in the axis of the vagina. Fundus was retroverted, normal in size and fairly movable. There was a left adnexal mass about 2 by 4 cm. prolapsed in the cul-de-sac. The right ovary was prolapsed, not enlarged. Right tube was palpable, probably clubbed. A diagnosis was made of sterility due to chronic adnexal disease occluding the tubes, and retroversion of the uterus.

On June 1, 1936, a Rubin test was negative at 180 mm. of pressure. Patient was then referred for treatment to the Sterility Clinic where she was given a course of diathermy treatments. A Rubin test repeated at this time was again negative.

She was then readmitted to the hospital for operation, which was done on Sept. 10, 1936.

The uterus was of normal size and third degree retroverted. Left tube was transformed into a hydrosalpinx, the ampullary portion being 4 cm. in diameter at its widest portion. The fimbriae were closed. The isthmic portion was occluded and the remainder of the tube was thickened. The hydrosalpinx was markedly adherent

*Presented at a meeting of the New York Obstetrical Society, February 14, 1939.

to the ovary and bound down in the cul-de-sac by adhesions. The right tube was thicker than normal and its fimbriated extremity was occluded. The ovary with the tube was prolapsed and adherent to the uterus.

Through a suprapubic midline incision, the adhesions about the right tube and ovary were freed by blunt dissection and the ovary and the tube brought up into the wound. Adhesions about the fimbriae were freed. Air was injected and the tube found to be patent. The adhesions about the left tube and ovary were freed and the large hydrosalpinx was dissected free, and on insufflation found to be also occluded in its inner third and therefore could not readily be reconstructed. It was then excised and the bleeding points clamped and ligated. The interstitial portion of the left tube was then reamed out with our specially devised reamer until the uterine cavity was entered. About one-third of the left ovary was resected and the freshly cut surface was sutured over the newly created uterine ostium with the use of double 0 interrupted chromic sutures. The right tube was then cuffed according to our method and suspended from the left wall of the pelvis by the Poole technique. The uterus was held out of the pelvis by a one point suspension, using a double No. 2 chromic suture. The abdomen was closed in the usual manner.

The postoperative convalescence was uneventful and the patient was discharged on Sept. 23, 1936. She reported to me Sept. 25, 1937, stating that her last period was on Aug. 14, 1937. A diagnosis of pregnancy of about six weeks was made, expected date of confinement being May 21, 1938.

The patient was admitted to our Obstetrical Service on May 10, 1938, at term with infrequent pains and at this time, although her pelvic measurements were normal, there was a question as to whether she was to be allowed to deliver spontaneously or whether a cesarean section was to be performed.

It is my feeling that a woman who subjects herself to any operative procedure in order to become pregnant is entitled to every chance for a living child. After consultation it was decided to perform a classical section. This was done on the morning of May 11, 1938, and a female child weighing 6 pounds 4½ ounces was delivered from the L.O.T. position. Upon inspection of the uterus it was found that the musculature was extensively thinned out near the fundus, especially where the Estes transplantation had been done at the left cornu. Finger inspection of the uterine cavity in this region disclosed that there was a cone extending up into the left cornu. What at one time consisted of the ovary was firmly incorporated on the left cornu of the uterus. The right tube was normal and the fimbriated extremity, where reconstruction had been done, was free. There were some fine filamentary adhesions to the posterior surface of the uterus. The uterus was closed in layers in the usual manner. Estimated blood loss was 400 c.c.

Patient's convalescence was uneventful. Both the mother and infant left the hospital in good condition on May 28, 1938. The mother has been seen at frequent intervals since the operation and a pelvic examination reveals that the uterus is in good position and no adnexal pathology is palpable. Where heretofore patient had complained of dysmenorrhea, she states that menstruation is now normal and free of pain. The baby is progressively gaining in weight and is in good condition.

CONCLUSIONS

It is my opinion that had this patient been allowed to go into labor, there might have been a disastrous result for both mother and infant due to the fact that the musculature of the fundus was markedly thinned out. It is difficult to decide whether the thinning out of the fundal uterine musculature in this particular case is due to the operative procedure or to an inherent condition of the uterine fundus. However, the decision to perform an elective cesarean section resulted in a most gratifying outcome and bears out the point which I wish to stress, that where a woman has been subjected to operative procedure for the cure of sterility and pregnancy ensues, an elective section is indicated in the interest of both mother and child.

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755 Park Avenue

INTERSTITIAL PREGNANCY FOLLOWING SALPINGECTOMY*

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Pregnancy in the interstitial portion of the Fallopian tube is a rather rare condition. Since 1893, when Traub and Lawson Tait performed the first operations for interstitial pregnancy, some 200 cases have been reported. Wynne[1] stated that, in his review of 3,982 cases of extrauterine pregnancy, there were 58 of the interstitial type, an incidence of less than 1.5 per cent.

Still more uncommon are cases in which the pregnancy occurs in the interstitial portion of the tube following salpingectomy. Richardson[2] and DiPalma[3] each report such a case.

The diagnosis, according to Ash[4] who reviewed the literature up to 1932, is seldom made prior to rupture, and more seldom is it made or even suspected preoperatively. Mathieu and Wilson[5] found that, of the cases reviewed by them, one-fifth were unruptured.

The case to be reported is one of unruptured interstitial pregnancy in the left cornu of the uterus, three years after a left salpingectomy had been performed for tubal pregnancy.

Mrs. F. P., aged 31 years, was first seen on Aug. 22, 1938, complaining of pain in the left side of the abdomen and vaginal bleeding. She stated that she was in her usual health until May, 1938, when she missed a menstrual period. The last period began on April 23, and was normal as to amount and duration. About June 16, she began to bleed and developed a dull aching pain in the lower left quadrant of the abdomen. The bleeding lasted about a week, and with its cessation the pain subsided. About July 11, the symptoms recurred and lasted seven days. She felt well except for occasional pain in the left side until August 17, when the bleeding recurred and the pain became constant and more severe.

Menses began at age of 13, regular, 28 days, lasting four to five days. The patient had been married 13 years, had 2 children living and well, and had not had any miscarriages. In November, 1935, she was operated upon for a left tubal pregnancy. The past history was rather eventful. She had the usual childhood diseases, an appendectomy in 1923, a cholecystectomy in 1928, erysipelas in 1932, and a left salpingectomy for a suspected tubal pregnancy in 1935. However, the gross and histologic examination did not substantiate this diagnosis.

The physical examination showed a fairly well-nourished young female who did not appear to be ill. The heart, lungs, blood pressure, temperature, pulse, and respiration were normal. The abdomen was marked by 3 operative scars and was soft throughout. There was considerable tenderness in the lower left quadrant. The vulva and vagina were negative. The uterus was normal in size and position, but its mobility was limited. There was a mass about the size of a lemon adjacent to the left cornu which seemed to arise from the uterus. The right adnexa were not palpable. The blood count showed 4.5 million R.B.C., 7,500 W.B.C., and 71 per cent polymorphonuclears, hemoglobin 72 per cent. Urinalysis was negative. The sedimentation rate was 23 mm. in sixty minutes. From these findings a provisional diagnosis of left cornual pregnancy was made and operation advised.

The patient was admitted to the Temple University Hospital on August 25, and on the next day a laparotomy was performed, excising the old left rectus scar. The peritoneum was incised and the pelvis explored. There was no free fluid in the

*Presented at a meeting of the Philadelphia Obstetrical Society, January 5, 1939.

peritoneal cavity. Several dense peritoneal and omental adhesions were encountered, cut, and ligated. The right tube and ovary were normal. The left tube was missing. The uterus was normal in size and position and presented a firm, irregular mass in the region of the left cornu. This mass consisted of ovary, omentum, sigmoid, and urinary bladder, adherent to each other and to the left cornu of the uterus. Dissection of this mass to free the intestine and bladder without perforation was accomplished at the expense of the uterine serosa, leaving a raw surface about 3 cm. in diameter on the fundus. The bleeding which resulted and the probability of the re-formation of adhesions at this point prompted the performing of a supravaginal hysterectomy and a left oophorectomy. The abdomen was closed in layers without drainage.

The patient had an uneventful postoperative course and was discharged on Sept. 8, 1938.

On Aug. 31, 1938, the following report was received from the pathologist. "The specimen consists of a uterus and ovary. The former is amputated above the cervix. It measures 8 by 5.5 by 4.5 cm. The wall is thickened and fibrotic. The left cornu of the uterine cavity leads directly into a large cystic cavity in the uterine wall. This cavity measures 2.5 cm. in diameter. The wall is lined with placental tissue and the lumen contains an 18 mm. fetus. The ovary is cystic. The block is quite cellular, although there is no evidence of malignancy or a corpus luteum."

This case of insterstitial pregnancy is reported, first, because of the rarity of the condition; second, because of the unusual circumstances surrounding this particular case; third, to re-emphasize the importance of history as a factor in the diagnosis of extrauterine pregnancy; and fourth, as a probable instance of intrauterine transmigration of the fertilized ovum.

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2118 PINE STREET

DISCUSSION

DR. HARRY A. DUNCAN.—Transmigration of that fertilized ovum from the right tube across the fundus into the left tube would seem established from this case. I had not previously been able to satisfy myself that a fertilized ovum could make this journey when it is so easy for it to slip out of the cervix. In this particular case, however, where the external opening of the left tube seems to have been sealed off, it seems that this must have occurred.

Dr. Forman was most fortunate in making the diagnosis early and giving the proper treatment. This was especially fortunate because the mortality in interstitial pregnancy is three times as great as in tubal pregnancy. An aid in making the diagnosis of interstitial pregnancy is the fact that it does not rupture so early as true tubal pregnancy. Many of the fine signs of an interstitial pregnancy, however, such as the elevation of the cornu, the fact that the fundus is pushed to the opposite side and that the tube appears to arise from the inferior surface of the mass, and the uterus is rotated because of the pull of the round ligament, are evident only after the abdomen has been opened.

DR. EDWARD A. SCHUMANN.—A problem of great interest is the mechanism and the frequency of external migration of the ovum. Many of the specimens in which this phenomenon is thought to have occurred present tightly sealed tubes or a completely closed amputated tube on the side from which the ovum is presumed to originate. Why is it not possible that the ovum springs from the ovary on the unaffected side, and after passing down the tube becomes implanted in the dilated uterine cornua on the opposite side?

DR. FORMAN (closing).—We probably would not have taken out this uterus under ordinary circumstances, but she started to bleed from the site where we had ripped off the uterine serosa. The hysterectomy was done only for that reason and not because we suspected that our preoperative diagnosis, cornual pregnancy, was still tenable.

INTERSTITIAL PREGNANCY*

Five Months' Gestation, With an Observation of the Phenomenon of Rupture at the Time of Operation

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(From the Department of Obstetrics, Cook County Hospital)

THE diagnosis of this type of tubal pregnancy before rupture is most difficult to make. Unless one has this condition in mind together with its criteria, the diagnosis may not be clear even at the time of operation, particularly if rupture has not occurred.

T. K., 27 years old, colored, married nine years, had not been able to become pregnant. She last menstruated on March 4, 1938. There were no unusual symptoms aside from right lower quadrant aches which were worse at the time of her menstrual molimina. She was first seen in the prenatal clinic of the Cook County Hospital on June 27, 1938 and no abnormal findings were detected at that time. On July 24, 1938, at 8 A.M., she experienced sharp cramplike pains that began five minutes after coitus. These pains were mostly in the right lower quadrant, but at noon their location shifted to the region of the naval, and later that day consisted of a dull pain and soreness in the epigastrium. The patient was admitted to the hospital at 2 A.M., on July 25, 1938, with a temperature of 100° F., pulse 120, of good quality, and respirations 24. The epigastric pains became more severe and she had some pain referred to both shoulders. The respirations soon became rapid (44 per minute), the breath sounds were diminished in the right lower portion of the thorax, and it hurt the patient to breathe deeply. One member of the resident staff thought that moist râles were present anteriorly. The abdomen was difficult to palpate due to muscular rigidity. There was a mass originating from the pelvis that reached the level of the naval but was mostly to the left of the midline. Fetal heart tones could be heard. Vaginal examination revealed a long rather narrow conical soft cervix. It was difficult to determine by bimanual palpation if the mass felt through the abdomen consisted of an intrauterine pregnancy that was deviated to the left, or whether the uterus, in view of a cervix being disproportionate in size to the entire mass, was separated from it. The red count was 3,850,000 late in the morning.

A diagnosis was deferred until the chest could be x-rayed. This was reported that afternoon to be negative. The condition of the patient was good; therefore, she was placed under close observation. However, when a repeated red cell count that evening showed a drop to 2,500,000, it was decided to open the abdomen. We felt certain that we were dealing with some form of ectopic pregnancy. A preoperative diagnosis of interstitial pregnancy was made purely through the clinical impression gained by the elimination of other related possibilities. Palpatory findings gave the impression that the pregnancy was not in the endometrial cavity. Intrauterine pregnancy was not considered because the cervix did not appear to be proportionate in size to a uterus of five months' gestation. Tubal pregnancy was excluded because of the rarity of such advanced gestation in the tubes. Abdominal pregnancy was considered, therefore, to be the only other possibility, but was not favored because the mass appeared to be too closely identified with the uterus itself.

At operation there was a moderate amount of free blood in the peritoneal cavity. The pregnancy was in the left uterine cornu and was unruptured. The left round ligament was at a higher level than the right one, and inferior and lateral to the site that contained the fetal sac. The left tube, which was normal, emerged from the side and inferior to the left angle. There was a small perforation on the posterior aspect of the uterine horn from which the patient was bleeding. In attempting to elevate the uterus to place clamps on the broad ligament for its amputation, the contents of the left uterine cornu began to rupture. This phenomenon consisted of a slow expression of the fetus in its amniotic sac which began at the point of

*Presented at a meeting of the Chicago Gynecological Society, December 16, 1938.

perforation. The process was rather slow and progressive and could not be checked, but when the fetal sac and placental remnants were separated and removed from the site of their implantation, the left uterine cornu had the appearance of a structure that had literally been exploded. The bleeding became profuse and the uterus was amputated supracervically. Transfusion of 600 c.c. of blood was started as the abdomen was being closed. The recovery was uneventful and the patient was discharged from the hospital fourteen days postoperatively.

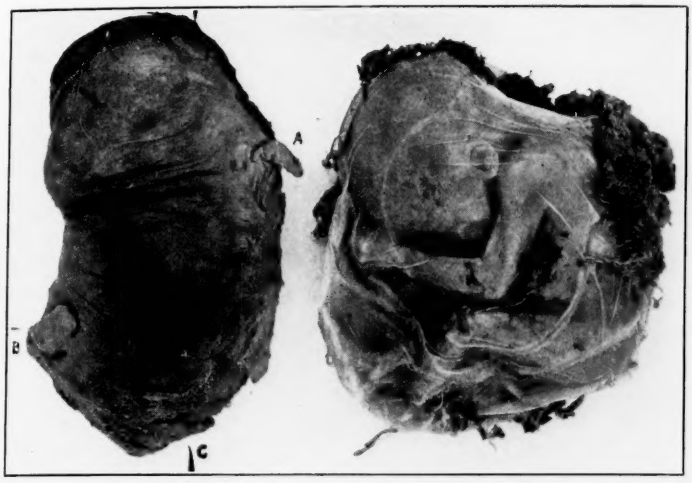

Fig. 1.—Anterior view of uterus showing the left round ligament (*A*), at a higher level than that on the right side, (*B*), and where the uterus was amputated (*C*). To the right the fetus is shown enclosed in the amniotic sac.

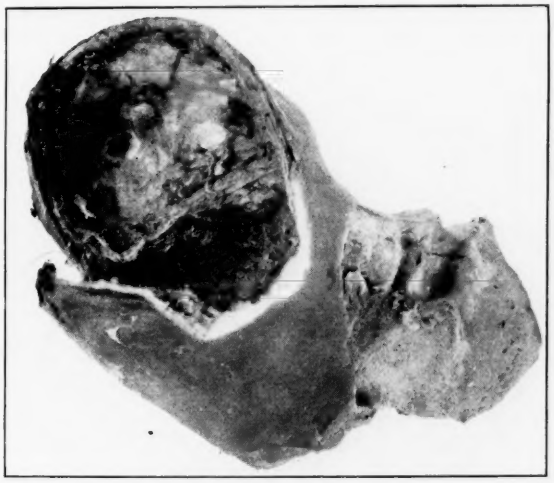

Fig. 2.—Posterior view of uterus showing the ruptured left uterine angle separated completely from the endometrial cavity (to the right).

The specimen consisted of the uterus in which the left broad ligament attachment was much longer than that of the right side. The appendages were therefore higher on that side. The cavity that contained the fetal sac was completely separated by a very thin septum from the uterine cavity. The fetus measured 16 cm. from head to rump.

185 North Wabash Avenue

A NEGLECTED SIGN FOR ROENTGENOLOGIC DIAGNOSIS OF INTRA-ABDOMINAL DERMOID CYST

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(From the Roentgenological Department of the Mount Sinai Hospital)

IN THIS short communication I would like to direct attention to a roentgenologic sign which, if present, permits an instantaneous anatomic diagnosis of an intra-abdominal dermoid cyst, even in such cases where the bony or dental anlagen of the tumor are not fully developed or escaped recognition by the roentgenologist.

The radiogram, Fig. 1, was taken of a patient, aged 25 years. It was the preliminary flat film of an intravenous urographic study ordered for differential diagnosis between a right ureteral concretion and a chronic recurrent appendicitis. The patient gave a history of attacks of pain over the right lower quadrant, radiating upwards to the right upper quadrant and at times associated with nausea and belching. These attacks occurred during the last two years once every three to eight months. Menstrual periods were regular, every four weeks, associated with a rather severe dysmenorrhea.

The x-ray film (Fig. 1) reveals a group of pathologic calcifications over the right wing of the os sacrum which is easily identified as teeth and bony structures. In addition, a fine regular, perfectly rounded, ring shaped shadow, as though drawn by a compass, is clearly visualized. This structure occupies the midportion of the pelvic cavity, emerges into the greater pelvis, and includes the above described calcifications. Its diameter is 13 cm., the breadth of the wall 1 to 3 mm.; the translucency for the x-rays is definitely increased inside the tumor upon comparison with the surrounding soft structures. The observation of a tumor giving a translucency instead of a density, at first thought, may appear very confusing; it is a well-established fact that solid tumors or cysts filled with liquid will cast a "shadow of soft tissue density" without any visualization of a wall except for pathologic calcifications. Since the structural detail of an x-ray picture, i.e., the appearance of shadows and translucencies of different intensity, is a direct function of the density of the transilluminated material, the conclusion must be drawn that the composition of the contents of the pathologic mass is the deciding factor.

According to Henke-Lubarsch's Handbook,[8] the contents of a dermoid are made up of, besides hair, an oily or fatty material, of a butter or vaseline-like consistency, and composed of neutral facts, fatty acid crystals, epidermis, cellular detritus, sweat drops, and occasionally cholesterin. The fatty portion has been found to be as high as 29.15 per cent. Since the density of fat is 533 (water 1000, blood 1027), a 30 per cent fat content in the cyst gives a very satisfactory explanation for a perceptible increase in its translucency on an x-ray film.

Following an analysis of 91 dermoids observed in 79 patients by Glass and Rosenthal,[6] hair and sebaceous material was found in 81, and sebaceous material alone in 6 specimens, giving a total of 95.5 per cent of cases where the roentgenologic sign of increased translucency could have been expected. Teeth were found in 18, bones in 13, teeth and bones in 8 specimens, giving a total of only 48.4 per cent of cases where the leading roentgenologic sign of the typical dental and bony shadows could have been expected. This survey shows that the "tumor of increased translucency," if looked for, should be observed twice as frequently as the shadows of teeth and bones in an abnormal location.

From the roentgenologic signs, a definite diagnosis of dermoid cyst of the ovary was made in our case and confirmed on operation. The specimen measured 12 by 8.5 by 10 cm., and was filled with a yellow greasy soft material mixed with hair. In one area, bone tissue and well-formed teeth were noted.

Upon careful study of the literature, no mention of this "ring shadow of increased translucency" in dermoid cysts was found among the numerous contributions in the last ten years on this subject. Two Swedish authors, Odquist[14] and Laurell,[10] observed this paradoxical sign and gave its correct interpretation. Among the three cases of Odquist, one presented a very diffuse limitation of the translucency without visualization of a capsule; on operation it was identified as a retroperitoneal lipoma.

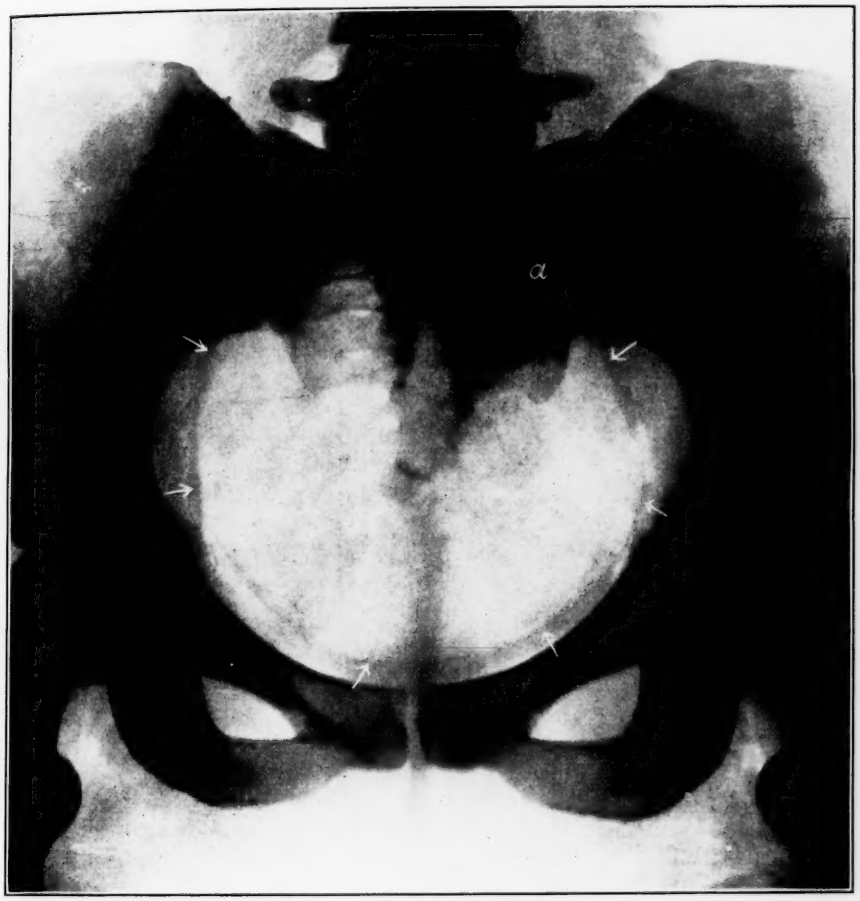

Fig. 1.—Dermoid of the right ovary. *a*, Dental and bony anlagen. Arrows point to the visible cyst wall. Note the increased translucency inside the tumor caused by the high fat content of the dermoid cyst.

In the other contributions on the roentgenologic diagnosis of intraperitoneal dermoid cysts, the interest was exclusively focused upon the visualization of teeth and bones in the abdominal cavity, and the old observation of Odquist and Laurell was completely neglected. Looking through the pictures published so far, poor quality of the reproductions in several contributions prohibits statistical evaluation of this sign. In some of the published radiograms, the demarcation of the large round translucency is striking (Aimé,[1] Heffernan,[7] Galifi[5]), but this was not mentioned in the x-ray reports of these authors.

A very interesting observation was reported by Phemister, Steen and Volderauer[15] on an intrathoracic dermoid cyst. Within the large round tumor shadow, a horizontal level was noted separating an upper zone of greater translucency from a

lower of greater density. This phenomenon was explained as produced by "a layer of liquid fat floating on aqueous fluid within the tumor." On the picture it is noteworthy how little difference there is between the translucency of the liquid intracystic fat and the surrounding areated lung tissue.

While in small dermoids with a diameter well within the range of a gas-filled bowel loop, this may easily be overlooked or misinterpreted, tumors of middle or large size should demonstrate the above described sign. Counting 1 case of Laurell, 2 of Odquist, 1 of Aimé, 1 of Galifi, 1 of Heffernan, and the case here reported, 7 conclusive observations are at hand for further study. As already mentioned, in the absence of teeth and bony structures without visualization of a capsule, differential diagnosis from a lipoma has to be made. There is a unique radiogram on record (Brown[2]), revealing a large, highly translucent ring shadow produced by a gas filled ovarian cyst from perforation of a diverticulum of the sigmoid into the cyst cavity. On operation the sigmoid loop was firmly adherent to the cyst, and a "great deal of foul-smelling fluid and gas was found within the cyst." This very rare condition can easily be differentiated by its very strong transillumination from the moderate translucency of a dermoid cyst.

SUMMARY

An intraperitoneal tumor which on a radiograph produces an increased translucency instead of a density is highly suggestive of a dermoid cyst. This becomes definite if the tumor wall itself is visualized. These findings will not be noted on an ordinary ovarian cyst or uterine fibroid. Differential diagnosis from lipoma and "gas filled ovarian cyst" is discussed.

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SIMULTANEOUS EXTRA- AND INTRAUTERINE PREGNANCY

Complicated by Acute Appendicitis and Tubal Rupture, Terminating With a Normal Intrauterine Pregnancy

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COINCIDENT or combined extra- and intrauterine pregnancy is thought to have been first observed at autopsy by Duverney in 1708. Since this first observation numerous cases have appeared in the literature, but cases which terminated with a living baby have been exceedingly rare.

In their compilation of 217 cases, Gemmell and Murray find 81 cases which terminated with a living baby, or were progressing normally with the intrauterine pregnancy at the time the case was reported. Since this exhaustive compilation in 1932, Bell, Banister, Bondurant and Weintraub have reported cases. The case here reported brings the number to 86.

As pointed out by Stein, an exact enumeration of cases of coincident or combined extra- and intrauterine pregnancy is exceedingly difficult because of the variety of captions under which they appear. Also, many cases have been reported with meager diagnostic and pathologic data so that there may be some doubt as to their eligibility. However, masterly efforts at compilation have been made by Zinke, Simpson, Neugebauer, Novak, Stein, and Gemmell and Murray and others. Zinke collected 88 cases in 1902 and Simpson 113 in 1904. The researches of Neugebauer raised the number to 244 in his second paper published in 1913. Novak, in 1926 adds 32 cases, including two of his own observation which had appeared in the literature subsequent to Neugebauer's compilation, making a total of 276 cases. Stein in 1928, without reference to Novak, adds 35 cases to Neugebauer's compilation, making a total of 279 cases. Stein's compilation includes 18 cases not found in Novak's which, added to Novak's, brings the total to 294 in 1928. By eliminating those cases not truly simultaneous as old ectopics complicating recent intrauterine pregnancy and other ineligible cases, Gemmell and Murray reduce the number to 217 cases. They reviewed the original report or an abstract of every case in the literature and their bibliography is apparently complete.

Novak finds 9 cases in which both extra- and intrauterine pregnancies went to term and both babies were delivered alive, the extrauterine by abdominal section. Bondurant and Weintraub report other cases, making 11 cases in which both intra- and extrauterine pregnancies produced a living baby. These 11 cases have been included in the above mentioned 86 cases terminating with a living baby.

CASE REPORT

Mrs. J. K., white, aged 21 years, was admitted to the Black Hills Methodist Hospital March 15, 1930 (Case No. 18042), with chief complaint of abdominal pain, very sharp, low in the abdomen, extending to the right side, and genital bleeding, since early morning. The pain continued with increasing severity until 12 M., when it was relieved for four hours by a hypodermic injection of morphine. At 4 P.M. the pain recurred with nausea and vomiting and continued with increasing severity until 8 P.M., when I saw the patient. She was admitted immediately to the hospital.

The patient had been married one year, had missed no periods, and no contraceptive methods were employed. Menstruation was normal, regular, twenty-eight-day type, four-days' duration, moderate flow and essentially painless. The patient had been exceptionally well until one month before, when she was shaken up in an automobile accident. Since the accident there had been a frequent appearance of a moderate genital bleeding. Five days before the bleeding became very profuse, accompanied by an acute abdominal pain. Both the pain and the bleeding quickly subsided and she felt very well until the onset of her present distress.

On examination the temperature was 99.4° F. by rectum, the pulse 80, good quality, the respiration 20. The abdomen was tender and slightly rigid on both sides below the navel, slightly more marked on the right side. Pelvic examination revealed the uterus enlarged above normal with definite softening of the cervix. The adnexa bilaterally were tender. There were no palpable masses but slight pressure upon the cervix elicited acute pain. Catheterized specimen of urine, turbid, light yellow, acid reaction, specific gravity 1.034, traces of albumin and acetone, occasional pus cell and few bacteria. Red blood cells 3,500,000, white 12,700. Provisional diagnosis, threatened abortion. One-fourth grain of codeine per hypodermic relieved the pain for several hours. A slight recurrence of pain the following day subsided without a sedative. Abdominal pain recurred March 17 at 9 P.M. Examination disclosed an increased tenderness in the right adnexa. The following morning at 4 A.M. pain became severe with nausea. Tenderness and rigidity had definitely localized over the cecal area. White cell count 15,700, red 3,100,000. Temperature 100° F. Diagnosis made of acute appendicitis complicating threatened abortion, and appendectomy advised. Surgery was declined. Ice bag, and ¼ gr. of codeine per hypodermic gave no relief. At 10 o'clock temperature rose to 102.2° F., pulse advanced to 110, and red cell count had decreased to 2,700,000. The patient was very

pale and very faint. Diagnosis of ruptured ectopic pregnancy with hemorrhage was made and consent for surgery obtained. Patient went to surgery at 11:30 A.M., March 18, 1930.

The abdomen was opened in the midline, revealing an extensive intraperitoneal hemorrhage. Examination of the uterus revealed a clot adherent to the right tube one inch from the uterine horn. Removal of the clot revealed complete amputation of the tube at isthmus by the rupturing ectopic. Both ends at the amputation were bleeding freely. The distal portion of the right tube and the right ovary were distended with hemorrhagic infiltration. The left tube was edematous and adherent to the left ovary. The uterus was enlarged.

Surgical procedure consisted of right salpingo-ovariectomy. Adhesions about the left ovary were liberated. Inspection of the cecum revealed a very acute appendix

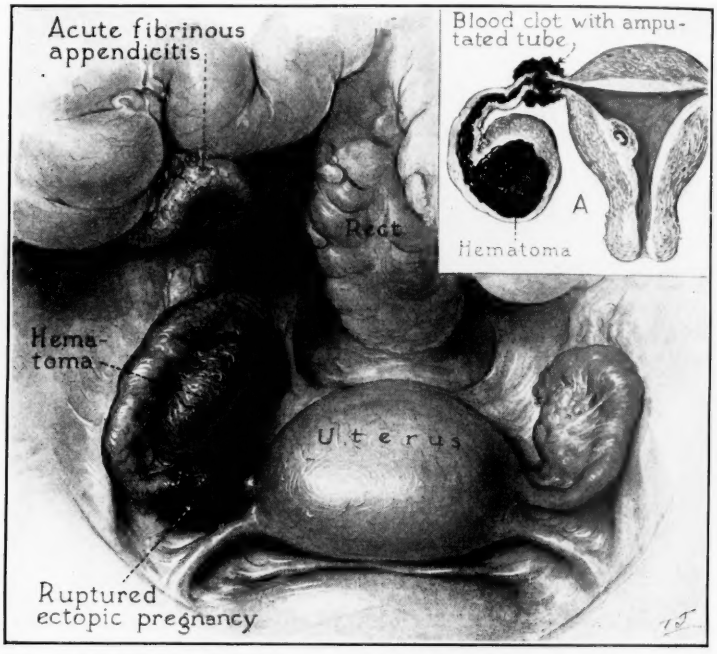

Fig. 1.—Illustration of the pathology as revealed upon intra-abdominal examination. *Insert A:* Diagrammatically showing extrauterine pregnancy in the isthmus of the right tube, complicating an intrauterine pregnancy. There was complete spontaneous amputation of the right tube at the isthmus by the expanding ectopic.

enveloped in its midportion by a thick, fibrinous exudate. The appendix was amputated and the ligated stump inverted with a purse-string suture of catgut. The abdomen was closed, with one large Penrose drain extending into the cul-de-sac.

Pathologic report: Hematosalpinx containing chorionic villi. Acute appendix.

Convalescence was extremely satisfactory. The temperature receded to 100° F. on the first postoperative day and became normal on the fourth. The patient was dismissed on the eleventh postoperative day.

The first postsurgical examination was made on April 25, four weeks after dismissal from the hospital. On pelvic examination, the uterus was about the size of an eight weeks' pregnancy. Diagnosis of intrauterine pregnancy was made and in retrospect a diagnosis of simultaneous intra- and extrauterine pregnancy. The patient positively stated that there had been no sex contact since her operation.

On Dec. 20, 1930 the patient was re-admitted to the hospital and delivered a normal female child weighing seven pounds and six ounces. The birth of the baby occurred just 277 days after her operation. Subsequently this patient had a second normal pregnancy, terminating with a healthy child. Her third pregnancy

terminated in abortion and the fourth was complicated by a left salpingitis for which she was operated upon by another surgeon, and this pregnancy also terminated in abortion at the fourth month.

SUMMARY

Using the compilation of Gemmell and Murray, the case reported is the eighty-sixth case of combined intra- and extrauterine pregnancy which terminated with a living baby. The complicating pathology which clouded the clinical picture enhances this rarity. The case was first diagnosed as pregnancy with threatened abortion. An acute appendix was next diagnosed as complicating a threatened abortion. Symptoms of concealed hemorrhage compelled a diagnosis of ruptured ectopic pregnancy. A complete spontaneous amputation of the right tube at the isthmus was found at operation. There was a complicating acute, fibrinous appendicitis. Pathologic examination demonstrated chorionic villi in the hematosalpinx. Diagnosis of intrauterine pregnancy was confirmed four weeks postsurgical by pelvic examination. The patient delivered a normal, female baby, weighing 7 pounds and 6 ounces, 277 days postsurgical. At present writing the product of this conception is a healthy, normal child.

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CHORIOANGIOMA OF THE PLACENTA

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WE WISH to describe the gross and histologic findings in a case of a chorioangioma of the placenta.

While tumors arising from the epithelial elements of the placenta, such as hydatiform mole, chorioadenoma, and chorionepithelioma are not uncommon, that neoplasm which apparently takes origin in the stroma of the chorionic villus, so-called chorioangioma, is of relatively infrequent occurrence. The first example of chorioangioma was described by John Clark in 1798. Up to 1924, Siddall collected 131 authenticated cases from the entire literature. In the past fourteen years, four additional reports have appeared in American journals.

Chorioangioma usually appears within the placenta as an elevation on the fetal side just beneath the amnion. Occasionally the tumor is pedunculated. The number may range from one to six; the size, from a millet seed to that of a child's head. Grossly, chorioangioma is a well-defined, solid tumor readily enucleated from the surrounding placental tissue, which is compressed to form a pseudocapsule. Regressive changes within the tumor itself including hemorrhage, pseudocyst formation, and calcification are known to develop. Thin septa often traverse the cut surface and produce a lobulated appearance. Blood vessels, after entrance into the tumor, run with the septa. Histologically, tumors demonstrate varying combinations of the following elements; blood vessels, fibrous, and myxomatous tissue, and, even, smooth

muscle fibers. Thus, from the microscopic picture, Dienst thought it appropriate to classify the altogether representative example of this group as capillary-hemangio-myxofibrosum-chorii.

Attention has been called to the presence of nucleated red blood cells within capillaries. Occasionally there has been noted endothelial proliferation with atypical cells and mitotic figures. Placental villi adjacent to chorioangioma reveal compression, and also degenerative changes; other neighboring villi may show increased number of ectatic capillaries in the stroma.

In its growth, the typical chorioangioma follows a benign course. Slight risk is involved for the mother unless the tumor reaches such size as to cause a mechanical obstructive dystocia. Vaginal bleeding is rarely an associated symptom. Chorioangiomas of large size, however, because of their frequent accompaniment with hydramnios and premature delivery, carry an increased fetal mortality that has been estimated between 30 and 40 per cent.

Mrs. R. K., a white, American housewife, 32 years of age, gravida ii, was admitted in labor to the Maternity Division of the Buffalo Children's Hospital on June 4, 1938. Abdominal examination disclosed a right occipitoanterior presentation and position; by rectal examination the cervix was felt to be half dilated.

Two hours following admission the membranes were ruptured artificially; a live normal male infant weighing 7 pounds 14 ounces was delivered spontaneously. The placenta and membranes were expelled completely following a modified Credé technique. Post-partum bleeding was estimated to be of normal amount. The puerperium was uneventful; the mother and child were discharged in good condition on June 16, 1938.

DESCRIPTION OF PLACENTA AND TUMOR

Macroscopic.—The placenta was discoid in shape. It measured 21 cm. in diameter and weighed 600 gm. The umbilical cord was inserted eccentrically 4 cm. from the margin. Situated on the fetal side of the placenta near the free margin was a hen's egg-sized mass measuring 9 by 6 by 4 cm., which caused a distinct elevation of the amnion. A thin layer of compressed chorionic villi measuring 0.2 cm. in width separated the tumor from the maternal surface. The tumor was well defined and could be easily shelled out from the surrounding tissues. Longitudinal section through the placenta revealed that the tumor was solid and firm. Toward the inner border was a hiluslike indentation into which placental tissue extended. Large blood vessels made their entry especially at the periphery of the tumor; fibrous tissue septa divided the tumor into lobules.

Microscopic.—The epithelium of the amnion covering the tumor was not well preserved. Between the amniotic surface and the margin of the tumor was a layer of loose connective tissue with cells showing elongated, dark-staining nuclei, and scattered cells with clear cytoplasm. The line of demarcation between the fibrous layer described and the tumor itself was regular and distinct. The tumor was composed of a sparse amount of connective tissue stroma and an abundance of capillary-sized spaces. These spaces were lined by endothelial cells which contained dark, spindle-shaped nuclei. In addition to these typical endothelial cells there was noted an occasional dark atypical cell; mitotic figures were not found. Many spaces were empty; others contained red blood cells. In still other spaces remnants of hemolyzed red blood cells were seen. A rare cell having the appearance of a nucleated red blood cell was observed. By special stain, the fibers in the stroma were shown to be chiefly collagenous and reticular. The pattern between the stroma and the spaces followed that of an angiomatous tumor. Scattered in the stroma were large cells with round, oval, or lobulated, usually eccentric nuclei, and with abundant, pink staining, sometimes foamy cytoplasm. By sudan stain yellow granules were demonstrated in the cytoplasm. In the indentations noted grossly lay placental tissue which showed ectasia of capillaries, necrosis, and focal calcification. Here amniotic epithelium was occasionally noted and the chorion was preserved.

In the hematoxylin and eosin stain, but especially in Van Gieson, Mallory, and modified Bielchowsky methods it was seen that the tumor was divided into lobules by

bands or trabeculae of somewhat compressed, chiefly collagenous connective tissue. Many fibers in the stroma of the tumor were in connection with these trabeculae. Some trabeculae contained blood vessels which had moderately thick walls. There were also found necrotic villi, villi with ectatic capillaries, and areas of focal calcification.

Fig. 1.

Fig. 2.

Fig. 1.—Placenta and tumor viewed from fetal surface.
Fig. 2.—Photomicrograph showing angiomatous structure of tumor.

Between the tumor proper and the placenta was a zone of compact fibrous tissue which contained large blood vessels. Here and immediately external to this zone were vessels showing thrombosis and calcification. The villi just adjacent to the tumor were compressed, and many showed regressive changes with organization of the stroma. Other villi showed an increased number of dilated capillaries. The intervillous spaces were narrowed and obliterated.

We are indebted to Dr. Kornel Terplan for his criticism and to Dr. Samuel Sanes for his assistance in preparation of this report.

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ENDOMETRIOMA OF LAPAROTOMY SCARS

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THIS case is presented to show the entire life history of an abdominal wall endometrioma, with a suggested method of prevention.

Endometrial tumors usually follow laparotomy involving uterine operations and in my opinion are due to faulty technique. Frequently an assistant clamps several of the bleeding uterine sinuses and instead of discarding the forceps used, will, later, when closing the abdominal wall, grasp the peritoneum or fascia with the identical instruments, thereby implanting endometrial tissue. This is what happened in my case when an inexperienced assistant committed this error in technique.

The easiest way to avoid this accident is to insist on using fresh clean abdominal pads and fresh unused sterile instruments and needles for the wound closure, and the surgeon and assistants should change their gloves. If the abdominal wound margins (before opening the uterus), were well protected (pads), and if the operator and assistants make a complete change of gloves, fresh instruments including needles and towels, then, abdominal wall endometrioma will indeed become a rarity.

Case Report.—A white female aged 34 years was delivered Sept. 4, 1930 by cesarean section. At 16 years of age she suffered a fall resulting in a fracture of her coccyx and sacrum which healed at such an angle that the head could not pass. After 12 years of married life she became pregnant.

On her nineteenth day, a small bleb exuding serum at the lowest angle and an indurated area near the upper third of the healed wound were noted but thought to be due to probable extrusion of catgut, which did not occur.

On the twenty-third day two small sinuses were present; the one nearest the center of wound had opened and was discharging clear serum and the induration had practically disappeared. Her vaginal flow was reddish and the color continued until the end of her thirty-sixth day. Only two tiny granulating areas remained on the fortieth day.

When the patient was again seen six months later, I found a pea-sized hard movable nodule in the midline corresponding to the sinus following operation. Removal was advised but the patient decided to wait.

Eight months following operation the patient came in and stated that "her irregular movable lump got sore and swelled up at menstrual time," but again she put off operation. A diagnosis of endometrioma was made.

Nine months after operation she again came in with a lemon-sized growth in the fat and down to fascia. The tumor had increased markedly in size in the last four months. It was plum colored and always became "very sore" at the menstrual periods. Operation again postponed.

Finally June 14, 1933, slightly more than two years and nine months following her cesarean operation, I performed an elliptical excision, including the umbilicus, followed by a vertical fascial overlapping and wound closure. A piece of omentum attached to overlying scar was removed intact. Uterus was normal and entire abdomen free of adhesions.

Pathologic Report (Dr. S. H. Gray).—A mass (lemon-sized) extended from just beneath the epithelium down almost to the rectus sheath; the mass was stony hard and of a brownish gray color, traversed by pale yellowish strands. Several dark blue cysts less than 1 mm. and a number of somewhat larger brownish gray cysts were seen. The mass did not appear to rise from the skin and the skin was somewhat movable over the mass. It was adherent at a single point to the rectus sheath which points through the abdominal wall to meet it.

Microscopic Findings.—From the deeper layers of the corium down to the peritoneum there were scattered areas of endometrial tissue containing many endometrial glands. Some of these glands were cystic and contained old blood. No endometrial tissue was found in the omentum adherent to the old scar.

At present time, January 1, 1939, this patient is in perfect health.

3615 OLIVE STREET

THE EDEMA OF ECLAMPSIA

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AN INCREASING amount of interest attaches to renal factors which may be concerned with the clinical features of eclampsia. The edema is of special interest because patients developing eclampsia are usually those who gain weight to an abnormal degree during pregnancy.

The renal pathology of eclampsia resembles that of nephrosis, and the edema of eclampsia like that of nephrosis has been attributed to the depletion of plasma protein from albuminuria.

Recently, another renal factor has been suggested as a possible contributory cause for edema in nephrosis.[1] It was suggested that the so-called degenerated epithelium of the convoluted tubules may be in a state of irritation and actually the site of excessive functional activity. An excessive capacity for secretion of ammonia into the urine was observed to be characteristic of nephrosis, and excessive resorption of water and sodium salts from the glomerular filtrate was thought to be a factor tending to aggravate the edema.

The present study deals with the activity of ammonia production in the special type of "degenerative" nephritis which is associated with eclampsia.

For details of the development of theory in the correlation of ammonia production with functional activity of the kidneys reference should be made to previous publications.[1, 2] It will suffice to indicate that a critical study of the ammonia mechanism has revealed that it fails to perform consistently in any manner which, according to conventional teaching, would tend to maintain body neutrality or to regulate the fixed base composition of the body fluids. Ammonia production is, however, constantly related to excess of strong acid over fixed base in the urine. For this reason it has been assumed that production of ammonia by the renal epithelium is a local protective mechanism which is stimulated by and tends to neutralize the acid fluid formed within the tubules by the resorption of sodium bicarbonate from the glomerular filtrate. This stimulus response conception led to the study of the ratio of ammonia to excess acid in the urine as an expression of functional activity of the renal epithelium, first in normal individuals, and then in different types of nephritis. It was observed that the excess acid was rather completely neutralized in concentrated urines of the normal controls; with active diuresis the neutralization was much less complete, presumably because of less intimate contact between acid and epithelium. And when the am-

monia ratios were plotted against rate of flow, a well-defined curved zone was obtained. The nephrosis ratios were over 100 per cent; in the chart they fell outside of the normal zone.

METHODS

The eclamptic subjects were patients having antepartum convulsions at term. They all had marked elevation of blood pressure, all had albuminuria and, with one exception, had pitting edema. The normal subjects were free of pitting edema and had no more than a trace of albumin in their urine; they also had no abnormal elevation of blood pressure.

Catheterized specimens of urine were obtained for the period, midnight to 6 A.M. Urinary acids and bases were determined by the methods of a previous publication.[1] The ammonia ratio was calculated from the equation:

$$R = \frac{NH_3}{(Cl + Po_4 + SO_4 + \text{organic acid}) - \text{fixed base}}$$

all expressed in M. Eq. per 100 c.c. urine. Rate of flow was calculated as cubic centimeters per kilo per hour. They are given in order that comparison may be made with the chart of the previous publication.

RESULTS AND DISCUSSION

It will be observed in Table I that the ratios for eclampsia are higher than those for normal pregnancy. Four out of five of the ratios for normal pregnancy are below 90 per cent; results such as were obtained previously for normal controls. Seven out of 9 of the antepartum specimens from eclamptic patients gave ratios over 100 per cent. Ratios above 100 per cent were previously observed in nephrosis. Such high ratios were interpreted to mean that the renal epithelium, because of a state of irritation, neutralized part of the weak organic acid as well as all of the strong acid. There is again, therefore, the suggestion of excessive tubular activity: excessive resorption of water and sodium salts as a contributory cause of scanty urine and edema.

The ratios obtained post partum were normal, and elevated flow rates indicate the onset of diuresis. Here there is the suggestion of a receding state of irritation.

Some comment should be made on the ammonia coefficients (NH_3/total N) observed by Williams in toxemias. With pernicious vomiting, the ratios were consistently high and in eclampsia they were frequently somewhat elevated.[3] To interpret these ratios it must be borne in mind that ammonia production varies directly with excess acid in the urine. With total nitrogen output constant, these ratios also vary with excess acid. Consequently, with a starvation ketosis such as develops with pernicious vomiting these ratios tend to be high. Observations have been made on one such patient. The ratio of NH_3/total N was over 30 per cent compared to a normal of about 5 per cent; the ratio of NH_3/excess acid was 115 per cent compared to a normal of about 100 per cent. The ammonia production in this case of pernicious vomiting was therefore such as we have frequently observed for eclampsia and nephrosis; and the renal pathology of pernicious vomiting is likewise similar to that of nephrosis and eclampsia.

TABLE I. AMMONIA RATIOS IN ECLAMPSIA AND NORMAL PREGNANCY*

SUBJECT	CHLORIDE	SULFATE	PHOSPHATE	STRONG ORGANIC ACID	FIXED BASE	EXCESS ACID	AMMONIA	RATIO %	RATE OF FLOW	COMMENTS
Ingl	9.64	3.55	1.23	2.08	11.28	5.22	5.63	108	0.94	Ante-partum specimen
Clara	2.12	8.38	3.33	9.19	17.50	5.52	6.52	118	0.35	Ante-partum specimen
Nan C.	1.92	2.14	0.54	3.20	5.68	2.12	2.27	108	0.66	Ante-partum specimen
Scott	14.08	6.16	0.77	9.14	26.78	3.37	3.78	112	0.45	Ante-partum specimen
Cotter	8.32	5.48	0.85	11.36	14.90	11.11	10.50	94	0.85	Ante-partum specimen
Lewis	5.01	3.72	2.49	4.21	6.05	9.38	7.95	85	1.15	Ante-partum specimen
Price	10.40	7.12	1.60	7.91	17.08	9.95	12.94	130	0.20	Ante-partum specimen
Ruth H.	2.12	1.59	1.76	1.88	3.94	3.41	3.54	104	0.60	Ante-partum specimen
White	0.96	5.25	1.22	2.80	7.14	3.09	3.74	121	0.29	Ante-partum specimen
Cozy C.	3.85	3.02	0.64	1.15	5.34	3.32	2.02	61	1.55	Second day post partum
D. But.	11.62	8.07	1.25	3.54	17.48	7.00	4.84	69	1.35	First day post partum
Cora W.	15.02	8.47	1.40	4.41	22.63	6.67	6.34	95	1.01	First day post partum
Smith	2.92	2.24	0.81	1.22	6.36	0.83	0.73	88	0.41	First day, no edema
Summ.	3.28	3.18	2.29	4.56	4.97	8.34	7.44	89	0.65	Normal pregnancy
Clark	10.60	2.04	2.22	2.52	14.20	3.18	2.72	85	1.40	Normal pregnancy
Keen	12.36	1.65	1.74	2.74	14.00	4.49	4.15	93	0.59	Normal pregnancy
Nabon	5.76	0.54	0.95	1.61	7.40	1.46	1.03	71	1.12	Normal pregnancy
Spears	21.60	1.25	1.27	3.73	25.56	2.29	2.01	88	1.00	Normal pregnancy

*Acids and bases expressed as M. Eq. per 100 c.c.

Most types of edema can be readily explained on a basis of a disturbance to the equilibrium between capillary blood pressure and the osmotic pressure of the plasma proteins. In eclampsia there is usually an increased venous pressure as well as a reduction of serum albumin;[4] each of these factors tends to produce edema. The female organism is, however, susceptible to fluctuations of water balance which are not so readily explained. At menstrual periods there is usually a definite increase in weight, presumably due to retention of water.[5] This possibly may be due to some influence of the pituitary on the renal epithelium leading to excessive resorption of fluid from the glomerular filtrate. In normal pregnancy there is a curious dilution of plasma electrolytes as well as of plasma protein.[6] This circumstance cannot be explained by any of the factors ordinarily considered, for none of them would tend to dilute the plasma electrolytes. Again there is the suggestion of distorted tubular resorption, possibly on an endocrine basis. In eclampsia there is a more definite expression of distorted tubule function in the excessive production of ammonia; an associated abnormality of tubular resorption is quite conceivable.

Of special interest is the question of an etiologic relation between the eclamptic convulsions and edema of the brain. It is realized that no close parallel holds between convulsions and subcutaneous edema, and that occasionally eclampsia occurs without visible edema. One of the patients of this series, L. S., had no edema, slight albuminuria, and total plasma protein was 6.4 gm. per cent; still she had antepartum convulsions associated with a rising blood pressure. We thought this was a case of eclampsia without edema. She had a normal puerperium.

Some light on the problem may be obtained by examination of other similar symptom complexes which are also associated with cerebral edema. In various types of anoxia, cerebral edema develops because of increased capillary permeability.[7] And the stimulation of brain centers in anoxia depends on the rate of development as well as the extent.[8] So a cerebral edema of small magnitude but developing abruptly might cause violent symptoms. Such a situation not infrequently occurs in acute nephritis where convulsions are associated with only slight nonpitting edema.

That an abrupt disturbance to the water balance does occur with convulsions in eclampsia is indicated by the work of Dieckmann,[9] who observed a decrease in blood volume and an increase in blood proteins to occur with the attacks. These findings indicate a change in capillary permeability with forcing out of plasma fluid into the previously well-filled extracellular spaces.

It seems most likely that the convulsions are precipitated by this factor which Dieckmann has discovered. But since the attacks occur most frequently in pregnancies with considerable edema, the factors of increased venous pressure, hypoproteinemia, and abnormal tubular resorption, must predispose by distention of tissue spaces.

Certain therapeutic implications appear to follow from the foregoing: sodium salts are restricted generally in any condition asso-

ciated with excessive extracellular fluid. The importance of sodium restriction in eclampsia has been emphasized by DeSnoo.[10] Strauss[11] has shown the beneficial influence of sodium restriction on both blood pressure and edema. Magnesium sulfate is of value as a diuretic; it appears to have a specific influence in reducing vasoconstriction and cerebral edema; it is of great value in controlling convulsions. As an adjunct to magnesium sulfate in sedation we prefer paraldehyde to morphine. Morphine causes too much respiratory depression, tending to produce anoxia which is decidedly undesirable for the reason that the concentration of blood observed by Dieckmann also tends to cause anoxia and myocardial embarrassment. We find that administration of oxygen is of definite value, for the fetus as well as the mother. Glucose in 10 per cent (sodium free) solution is administered intravenously as a heart tonic, to facilitate diuresis, and for calories.

SUMMARY

In eclampsia, as in nephrosis, there is an excessive activity in production of ammonia by the kidneys. It is suggested that excessive resorption of glomerular fluid is a contributory cause of scanty urine and edema in eclampsia.

The relation of the edema to certain clinical features of eclampsia is discussed.

REFERENCES

(1) *Briggs, A. P.:* Arch. Int. Med. **60:** 193, 1937. (2) *Briggs, A. P.:* J. Biol. Chem. **104:** 231, 1934. (3) *Williams, J. Whitridge:* Obstetrics, ed. 3, New York and London, 1912, D. Appleton-Century Co., p. 525. (4) *Strauss, M. B.:* Am. J. M. Sc. **190:** 811, 1935. (5) *Sweeney, J. S.:* J. A. M. A. **103:** 234, 1934. (6) *Oard: H. C., and Peters, J. P.:* J. Biol. Chem. **81:** 9, 1929. (7) *Landis, E. M.:* Am. J. Physiol. **83:** 528, 1927-28. (8) *Gasser, H. S., and Loevenhardt, A. S.:* J. Pharmacol. & Exper. Therap. **5:** 239, 1913-14. (9) *Dieckmann, W. J.:* Am. J. Obst. & Gynec. **32:** 927, 1936. (10) *DeSnoo, K.:* Ibid. **34:** 911, 1937. (11) *Strauss, M. B.:* Am. J. M. Sc. **194:** 772, 1937.

Johnson, C. R.: Pelvimetry by Stereoroentgenometry. Am. J. Roentgenol. **38:** 607, 1937.

Stereoroentgenometry offers a practical method for the application of roentgenology in obstetrics. The obstetrician who depends upon external measurements of the maternal pelvis for his information as to deformity or contracture of the birth canal leans upon a weak staff. It is probable that if he guessed all his patients normal and made no measurements at all he would be right in a much higher percentage of cases. If he measures the diagonal conjugate and the bisischial diameters by his best available clinical methods he will probably find those cases which might have dystocia. If he takes this latter group in which he finds clinical evidence of abnormality and has them subjected to careful roentgen study, he will find that about one out of every three actually have abnormalities and will require special attention. Stereoroentgenometry offers a method for determination of the solid dimensions of radiopaque objects from their stereoscopic roentgenograms. It is useful because it is practical.

J. P. Greenhill.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF DECEMBER 13, 1938

The following papers were presented:

Report of a Case of Ovarian Teratoma. Dr. Thos. C. Peightal.

The Treatment of Dysmenorrhea With Testosterone Propionate. Drs. U. J. Salmon (by invitation), S. H. Geist, and R. I. Walter (by invitation). (For original article, see page 264.)

MEETING OF JANUARY 10, 1939

The following papers were presented:

Toxemia of Pregnancy. Dr. Maurice B. Strauss, Boston (by invitation). (For original article, see page 199.)

Extraperitoneal Cesarean Section, With the Presentation of a New Technique. (Moving picture demonstration.) Dr. Edward G. Waters.

MEETING OF FEBRUARY 14, 1939

The following papers were presented:

Pregnancy Following Modified Estes Ovarian Transposition and Cuff Operation on Oviduct. Dr. Francis W. Sovak. (For original article, see page 342.)

Hormone Factors in the Toxemias of Pregnancy. Drs. H. C. Taylor, Jr., and Eugene N. Scadron. (For original article, see page 963, June, 1939.)

Studies on Reconstruction of the Fallopian Tube. Dr. J. Randolph Gepfert. (For original article, see page 256.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF JANUARY 5, 1939

The following papers and discussions were presented:

Interstitial Pregnancy Following Salpingectomy. Dr. Isador Forman. (For original article, see page 344.)

Severe Menorrhagia as the Only Symptom of Essential Thrombocytopenic Purpura Cured by Splenectomy. Drs. S. Leon Israel and Theodore H. Mendell (by invitation). (For original article, see page 339.)

Report of a Series of Thirty-Five Cases of Primary Malignancies of the Ovaries. Dr. Theodore Cianfrani (by invitation).

Macrocytic Anemia of Pregnancy and Anemia of the Newborn. Drs. Joseph A. Ritter (by invitation), and Walter J. Crocker (by invitation). (For original article, see page 239.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF JANUARY 20, 1939

The following papers were presented:

The Obstetric Management of Patients with Toxemia. Drs. W. J. Dieckmann and Ira Brown (by invitation). (For original article, see page 214.)

The Treatment of Early Abortion. Drs. C. E. Galloway and T. D. Paul. (For original article, see page 246.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Labor

Fredrikson, H.: The Effect on Deliveries of Spontaneous Rupture of the Membranes, Acta obst. et gynec. Scandinav. **17**: 309, 1937.

The author studied 1,290 primiparas and 1,300 multiparas who had normal occipitoanterior presentations in which the babies weighed over 2,500 gm., to determine the effect of spontaneous rupture of the membranes on labor. As "premature rupture" he designates cases in which rupture occurred before or simultaneously with the onset of pains. The term "early rupture" is used to indicate rupture of the bag of waters after the onset of pains but before the cervix is dilated to the size of three fingers. The author found that rupture of the membranes occurred before the onset of pains in 12 per cent of primiparas and in 10.7 per cent of multiparas. Rupture of the bag of waters occurred simultaneously with the onset of pains in 7.8 per cent of primiparas and in 5.7 per cent of multiparas. In both primiparas and multiparas the duration of labor was considerably shortened in cases of premature rupture of the membranes. In primiparas, labor was definitely prolonged in cases of early rupture. Genital infections during labor occurred twice as often in cases of premature and early rupture as in the cases of late rupture. The fetal mortality was not increased in cases of premature rupture, but it was higher in cases of early rupture.

J. P. GREENHILL

Apajalahti, A.: Is the Time of Rupture of the Membranes Dependent Upon the Histologic Structure of the Membranes? Acta obst. et Gynec. Scandinav. **18**: 57, 1938.

This investigation verifies the fact that rupture of the bag of waters during labor bears a definite relation to the histologic structure of the fetal membranes especially to the thickness of the amnion. The thinner the membranes are, especially the amnion, the more pronounced are the degenerative changes, and the easier it is for the membranes to rupture. The author could not find any evidence that inflammation produced any adhesions between the membranes and the decidua.

J. P. GREENHILL

Wetterdal, P.: Some Notes on the Premature Rupture of the Membranes, Acta Obst. et Gynec. Scandinav. **18**: 45, 1938.

The author studied a series of 1,022 cases in which liquor amnii was expelled before the onset of labor pains. He found two classes of patients. In the first group labor was short and there were few complications, while in the second group delivery was delayed and there were numerous complications. The author believes that the responsible factor for the complications in the second group is not the premature rupture of the bag of waters but the ineffectual labor pains which occur in this series.

A vaginal examination in 150 cases of premature rupture of the membranes revealed that in some of these cases a certain amount of labor had occurred without the patient's knowledge. In a series of 312 cases of premature rupture of the membranes the author not only studied the mothers but also the children

up to twelve years of age. In this series, there were 221 spontaneous deliveries and 91 forceps operations. The author found that premature rupture of the membranes affects neither the maternal mortality nor the health and mentality of the offspring.

J. P. GREENHILL

Smythe and Thompson: Induction of Labor by Rupture or High Puncture of the Membranes, J. Obst. & Gynaec. Brit. Emp. 44: 480, 1937.

Induction is performed in one of two ways: The first is by simple rupture of the membranes at the internal os, and is done with or without anesthesia. A volsellum is employed to tear the membranes, and liquor allowed to drain by slightly pushing up the fetal head. In this way the amount can be roughly controlled.

The other method, viz., high puncture of the membranes, is performed as follows: One finger is inserted into the cervix and passed up until the head can be felt. The S-shaped cannula is then passed up the finger until it meets the head and then passed between the membranes and the uterine wall above the head when the membranes are punctured by pressing home the stylet. This can also be done with or without anesthesia, as indicated in each particular case. The special advantage of this method is that the chances of infection of the liquor are greatly diminished, which is of great importance should cesarean section become necessary in the course of a trial labor.

In the Bristol General Hospital series of 210 consecutive labors all the cases of induction by artificial rupture of the membranes at the os were successful and only one induction with the cannula failed.

The duration of labor is not appreciably lengthened. Stillbirth rate and the likelihood of sepsis are not increased. In this series 91.4 per cent of the cases had unassisted deliveries.

J. P. GREENHILL

Thoms, Herbert: The Obstetrical Significance of Pelvic Variations, Brit. M. J. 2: 210, 1937.

The report is given of an x-ray study of 450 primiparous white women delivered at term in the New Haven Hospital.

The "grid method" of pelvimetry originally developed by Thoms was used. In addition, lateral aspects of pelvic roentgenometry were employed, as well as a newly modified technique for lateral viewing.

The author classifies the pelvis into four types:

1. Dolichopellic or anthropoid type. The anteroposterior diameter is longer than the transverse.

2. Mesatipellic or round type. The anteroposterior diameter is equal to or slightly less than the transverse (never more than 1 cm.).

3. Brachypellic or oval type. The anteroposterior diameter is between 1 and 3 cm. shorter than the transverse.

4. Platypellic or flat type. The anteroposterior diameter is excessively shorter than the transverse, 3 cm. or more.

On the basis of the length of the anteroposterior diameter, the first three groups may be divided for clinical use into large, average, and small pelves which classification serves to depict the shape of the superior strait. The external measurements bear no relation to those of the superior strait by roentgenometry.

The incidence of the various types is recorded. The author finds that the round type predominates.

This study calls for a reconstruction of views regarding normal white female pelves, as evidenced by the presence of the oval or brachypellic type in only 35 per cent of cases. The chief value of roentgenometry is in cases of suspected disproportion. Here the lateral technique is of great importance.

Routine use of x-ray in primiparous women is justified and serviceable.

F. L. ADAIR AND S. A. PEARL

Greulich, W. W., and Thoms, Herbert: The Dimensions of the Pelvic Inlet of 789 White Females, Anat. Rec. 72: 45, 1938.

More or less coinciding with the dimensions given in most textbooks, more recently, Jarchow (1933) from a compilation of several large series of measurements of pelves of European women concluded that a conjugate of from 11.0 to 11.5 cm. and a transverse diameter of 13.5 cm. for the pelvic inlet may be considered as normal.

Such dimensions so far had been determined on cadavers and dried pelves. In the belief of the authors methods of roentgen pelvimetry have developed now to such a degree of exactness that dimensions obtained in this manner must be accepted as accurate. The authors summarized their findings in approximately 600 primigravidas and 100 nulliparous, well-developed young women (student nurses).

Their results are striking. In 37 per cent of nurses the conjugate of the inlet was larger than the transverse diameter. This same relation was ascertained, e.g., among 132 clinic patients, in only 13.6 per cent. The transverse diameter exceeded the conjugate by more than 1 cm. in only 17 per cent of the nurses as compared with 40.1 per cent among clinic women. In only 6 per cent of the nurses and 14.9 per cent of the clinic patients the excess of transverse over conjugate diameter was more than 2 cm., and thus large enough to fit the textbook description of the "normal" pelvis.

Some of the final conclusions are of interest to the obstetrician.

The type of pelvis, which for the past two centuries has been considered normal for white women, was found in less than 15 per cent of 582, primiparous clinic patients, and in only 6 per cent of 100 young women from a much more privileged economic group. It was, therefore, neither the normal pelvis, in the sense of being the most frequently occurring type, nor was it the most adequate type, as gauged by the relative frequency of operative interference required during labor.

It has been known for a long time that marked anterior-posterior flattening of the adult pelvis may result from severe rickets during early life. The high incidence of round and of antero-posteriorly elongated pelves among the nurses suggests the possibility that adequate nutrition during early life and other factors which make for attainment of maximum, normal body size prevent that degree of anteroposterior flattening of the pelvis which has come to be regarded as characteristically feminine.

HUGO EHRENFEST

Moller-Christensen, E.: The Course of Pregnancy, Labor, and Puerperium in Overweight Primiparas, Acta obst. et gynec. Scandinav. **18**: 222, 1938.

A series of 242 overweight primiparas was studied by the author, who considered a woman overweight if at the end of pregnancy she weighed at least 20 per cent more than a nonpregnant woman of her age and height. He compared this series with another consisting of 500 women not one of whom weighed over 70 Kg. (154 pounds). The author found ordinarily that obese patients are more frequently sterile than women with normal weights. Nephritis occurred in 21.4 per cent of the overweight women and eclampsia in 7.2 per cent. On the other hand nephritis occurred in only 1.6 per cent of the women with normal weights and there was not a single case of eclampsia in the latter group. Hypertension occurred in 6.2 per cent and 0.4 per cent, respectively, in the two groups. Likewise pyelitis was found in 11.6 per cent of the overweight group and in only 4.8 per cent of the control group.

During labor there were more complications in the overweight group, especially uterine atony. These lead to a greater frequency of post-partum hemorrhage, retained placentas, and manual removal of the placenta.

Labor lasted, on an average, 27½ hours in the overweight women and only 13½ hours in the others. Uterine atony occurred in 18.4 per cent and 4.4 per cent, respectively, of the author's cases. Premature rupture of the membranes occurred in 14.8 per cent and 4 per cent, respectively. Fever occurred in 8.7 per cent and 0.6 per cent, respectively.

Babies weighing 4,000 gm. and more were born to 24.7 per cent of the overweight group and to only 4.4 per cent of the control series. The fetal mortality in these two groups was 6.7 per cent and 0.6 per cent, respectively.

J. P. GREENHILL

Reist, A.: Significance of Manual Dilation of Os Uteri in Treatment of Disturbances in Dilatation of Soft Parts During Birth, Schweiz. med. Wchnschr. **66:** 1176, 1936.

If a careful technique is employed and asepsis is preserved, manual dilatation of the os uteri produces in suitable cases the desired results, that is, rapid termination of the period of dilatation. It is helpful in certain cases in which dilatation is retarded or has completely stopped, because it permits spontaneous delivery in a manner that involves no danger for either mother or child. Manual dilatation of the os uteri can be used also for rapid opening of the soft parts for the purpose of an immediate delivery in cases in which danger appears suddenly for either mother or child. Reist uses this procedure in 4-6 per cent of all deliveries. Its correct employment reduces the number of extensive vaginal obstetric interventions as well as infant mortality during birth.

J. P. GREENHILL

Taylor, H. C., Jr.: Indications and Technic of Episiotomy, Am. J. Surg. **35:** 403, 1937.

Correct use of episiotomy forms one of the niceties of obstetric practice. The consideration of whether to undertake the operation in a given case demands balancing of a known type of surgical injury against an unknown degree of trauma from the stretching effects of the presenting part against the perineum. Regret for having performed needless episiotomy is probably less frequent and certainly less permanent than that experienced at times for having omitted it.

J. P. GREENHILL

Jahier: Fifty-Seven Breech Deliveries, Bull. Soc. d'obst. et de gynéc. **26:** 615, 1937.

Among the 57 breech presentations reported by the author there were 35 primiparas and 22 multiparas. There was no maternal mortality in this series but three babies were lost. The author makes a few recommendations. Among these are that two obstetricians be present in cases where difficulty is expected, so that they may take turns in executing the delicate maneuvers necessary for delivery of the child. An episiotomy should be done routinely and in many cases it should be bilateral. The author recommends that thin gloves be used and that they should be well lubricated. He also urges that all equipment be at hand for the resuscitation of the newborn.

J. P. GREENHILL

Macafee, C. H. G., and McClure, H. I.: A Critical Survey of 349 Cases of Breech Delivery, Brit. M. J. **2:** 1112, 1937.

Three hundred and forty-nine cases of breech delivery formed the basis for the following conclusions: 305 were primary breech presentations. In all, 332 mothers were delivered of 349 babies, i.e., there were seventeen cases of twins in which each child was delivered by breech. Outside of 3 cesarean sections, all deliveries were performed by usual methods. The gross fetal mortality was 33.8 per cent, being 23.72 for primiparas and 38.96 per cent for multiparas. Corrected rates, eliminating those cases in which the death of the fetus was not primarily or directly due to the breech presentation, gave a 10 per cent fetal mortality for primiparas and 3.42 per cent for multiparas.

In summarizing their management of breech presentation, they strongly recommend external version after the thirtieth week in all cases and not later than the thirty-fourth in multiparas.

In breech delivery the authors interfere only when the breech has ceased to advance. Episiotomies are done on all primiparas and when necessary in multigravidas. They urge that the operator refrain from interfering with normal mechanisms pointing out that slow and gentle deliveries prevent tentorial tears, and these tears are much more likely to cause death of the fetus than asphyxia, the excuse for rapid delivery.

F. L. Adair and J. A. Haugen.

Chamanlal Mehta: External Version for Breech Presentations, Brit. M. J. **1:** 706, 1937.

The author presents an analysis of 5,028 deliveries in which two groups are discussed. Group I consists of 3,240 deliveries in which breech presentation was recognized and not interfered with during pregnancy. Eighty-eight women were confined as breech deliveries, an incidence of 2.7 per cent, and the fetal mortality in this group was 37.5 per cent. Of the 88 breech presentations 21 were in primiparas, with a fetal mortality of 33.3 per cent and 67 in multiparas with a fetal mortality of 38.8 per cent.

In the second group of 1,788 consecutive deliveries, breech presentation was diagnosed in 110 cases, but only 11 of them became breech deliveries, i.e., 0.06 per cent. Fifty-five were treated by external version during pregnancy. The fetal mortality in this series of 110 cases was 4.54 per cent, and all the deaths were in the untreated cases. There was no mortality in the cases managed by external version. The fetal mortality of 37.5 per cent in Group I should be compared with that of 4.54 per cent in Group II with no mortality in cases treated by external version.

The questions of prematurity, when to perform external version, its possible dangers and the technic are briefly discussed.

F. L. Adair and S. A. Pearl.

Casalta: External Version Followed by Abruptio Placentae, Bull. Soc. d'obst. et de gynec. **27:** 73, 1938.

The author reports a case of breech presentation in which he performed an external version. This was done very gently and the fetal heart tones were normal after the procedure. However six hours later the patient had uterine contractions and a profuse hemorrhage. The uterus became hard and a few hours later a stillborn child was born. Two large clots were found in depressions in the placenta.

The author believes that the external version resulted in the separation of the placenta and death of the baby.

J. P. Greenhill.

Bruecke, H. v.: High Forceps Operations, Arch. f. Gynäk. **164:** 42, 1937.

An analysis of 18,611 deliveries in the Graz Frauenklinik showed a total forceps incidence of 2.1 per cent and a high forceps incidence of 0.18 per cent (34 cases). Among these latter 34 women there was no maternal mortality, but five suffered extensive lacerations of vagina and rectum, and two developed vesicovaginal fistulas following pressure necrosis in one and laceration in the other. Both fistulas healed spontaneously. Fourteen of the 34 babies died and 11 had severe head injuries. Most of these occurred in women with contracted pelves. In spite of the above results, the author believes that there is a definite even though only occasional indication for high forceps delivery. In such instances the Kielland forceps are the instruments of choice.

Ralph A. Reis.

McIlroy, Louise: Surgical Intervention in Obstetrical Practice, Brit. M. J. 1: 800, 1937.

A brief discussion is given of the indications for and against surgical intervention in obstetric practice from the standpoint of the general practitioner. The wider the experience one has gained in the management of obstetric cases, the more conservative one generally becomes.

Maternal mortality records from all parts of the world prove that conservative methods in obstetrics furnish the most favorable results. Not infrequently many an obstetrician has faced the problem of gathering courage to leave well enough alone, rather than terminate pregnancy or labor by some operative method. The author's rule is "when in doubt do nothing," and "wait and see" is not a bad rule to follow in obstetrics. It is the exercise of wise judgment, however, that really gives good results.

Antenatal complications are discussed. Intervention during labor, the management of the third stage, and puerperal sepsis are treated briefly.

F. L. ADAIR AND S. A. PEARL.

Stapleton, Grace: Rupture of the Pregnant Uterus From Indirect Injury, Brit. M. J. 2: 367, 1937.

The author reports a case of complete rupture of the uterus from indirect injury in a primigravida of 17 years. The fall from a 12 foot high veranda occurred some ten days before term. The patient was ill for several days in bed with vomiting and slight pain but later showed no alarming symptoms of a grave injury. The patient failed to go into labor after two medical inductions at which time the correct diagnosis was established. Laparotomy with extraction of the baby from the abdominal cavity and subsequent rapid repair of the ruptured uterine wall was followed by recovery, although surgery was undertaken fourteen days after the injury. The patient did not show the classical signs and symptoms of a ruptured uterus.

F. L. ADAIR AND S. A. PEARL.

Items

American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 6, 1940, at 2:00 P.M. *The Board announces that it will hold only one Group B, Part I, examination this year prior to the final general examination, instead of two as in former years.* Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held in June, 1940.

Applications for admission to Group B, Part I, examinations must be on file in the Secretary's office not later than October 4, 1939.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Applications for admission to Group A, Part II examinations must be on file in the Secretary's office not later than March 15, 1940.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I examinations (written paper and case records) and the Part II examinations (pathological and oral).

At the annual meeting of the Board, held in St. Louis on May 12, 1939, it was found necessary, on account of increased administrative expenses, to increase the application and examination fees. Effective May 12, 1939, these are as follows: Application fee $15.00, payable upon submission of application for review by Board; examination fee $85.00, payable upon notification to candidate of acceptance of the application and assignment to examination. Neither fee is returnable. This increase does not apply to candidates whose applications were filed prior to May 12, 1939.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Pacific Coast Society of Obstetrics and Gynecology

The dates for the next meeting of the Pacific Coast Society of Obstetrics and Gynecology have been changed from October 4 to 7, 1939 to November 8 to 11, 1939 in Portland, Oregon.

Central Association of Obstetricians and Gynecologists

The Eleventh Annual Meeting of the Central Association of Obstetricians and Gynecologists will be held at the Hotel Muehlebach, Kansas City, Mo., November 2, 3, and 4, 1939. The guest speaker will be Dr. Edward A. Schumann, of Philadelphia, Pa.

Books Received

THE GENUINE WORKS OF HIPPOCRATES. Translated from the Greek by Francis Adams, LL.D., Surgeon. The Williams & Wilkins Company, Baltimore, 1939.

RECENT ADVANCES IN OBSTETRICS AND GYNAECOLOGY. By Aleck W. Bourne, Obstetric Surgeon to St. Mary's Hospital, etc., and Leslie H. Williams, Senior Obstetric Surgeon to Out-Patients, St. Mary's Hospital, etc., University of Cambridge. Fourth edition, with 98 illustrations, 366 pages. Blakiston's Son & Co., Philadelphia, 1939.

CLINICAL PATHOLOGICAL GYNECOLOGY. By J. Thornwell Witherspoon, Formerly Associate Professor of Experimental and Pathological Gynecology, Indiana University Medical Center, Indianapolis. Illustrated with 271 engravings, 400 pages. Lea & Febiger, Philadelphia, 1939.

TEXTBOOK OF GENERAL SURGERY. By Warren H. Cole, Professor of Surgery, University of Illinois, College of Medicine, etc., and Robert Elman, Associate Professor of Surgery, Washington University School of Medicine, St. Louis. Second edition, 559 illustrations, 1031 pages. D. Appleton-Century Company, New York, 1939.

SEX AND INTERNAL SECRETIONS. A Survey of Recent Research. Editors: Edgar Allen, Yale University; Charles H. Danforth, Stanford University; and Edward A. Doisy, St. Louis University, with foreword by Robert M. Yerkes, Yale University. Second edition, illustrated, 1346 pages. Williams & Wilkins Company, Baltimore, 1939.

VERHUETUNG ERBKRANKEN NACHWUCHSES. Eine kritische Betrachtung und Wuerdigung. Herausgegeben von Dr. St. Zurukzoglu. 346 pages. Verlag von Benno Schwabe, Basle, 1938.

ENDOCRINOLOGY IN MODERN PRACTICE. By William Wolf, Endocrinologist to the French Hospital, etc. Second edition, completely revised. 176 illustrations, 1077 pages. W. B. Saunders Company, Philadelphia, 1939.

DIE ALLGEMEINBETAEUBUNG NACH IHREM HEUTIGEN STAND. Dr. Richard Goldhahn, Chefarzt des Kreiskrankenhauses Liegnitz. With 10 illustrations, 79 pages. Verlag von Ferdinand Enke, Stuttgart, 1939.

GYNAECOLOGY. By Herbert H. Schlink, Lecturer and Examiner in Gynaecology, University of Sydney, etc. 179 illustrations, 557 pages. Angus & Robertson Limited, Sydney, 1939.

A TEXTBOOK OF OBSTETRICS, With Special Reference to Nursing Care. By Charles B. Reed, Associate Professor of Obstetrics, Northwestern University Medical School, etc., and Bess I. Cooley, R. N., Supervisor and Instructor, Department of Obstetrics, Wesley Memorial Hospital, Chicago. With 209 illustrations, 476 pages. The C. V. Mosby Company, St. Louis, 1939.

THE CLINICAL AND EXPERIMENTAL USE OF SULFANILAMIDE, SULFAPYRIDINE, and Allied Compounds. By Perrin H. Long, M.D., Associate Professor of Medicine, School of Medicine, Johns Hopkins University, etc., and Eleanor A. Bliss, Sc.D., Fellow in Medicine, Johns Hopkins University. 319 pages. The Macmillan Company, New York, 1939.

HANDSCHRIFT UND EIGENART DER KREBSGEFAEHRDETEN. Ein Beitrag zur Dispositionsforschung. Illustrated, 297 pages. Verlag von Brueder Tisza, Budapest, Hungry. (T. H. McKenna Inc. 878 Lexington Ave., New York, N. Y.).

SYPHILIS, and Its Accomplices in Mischief: Society, State and Physician. By George M. Katsainos. Privately printed at Athens, Greece. 1939.

DIE KREUZSCHMERZEN DER FRAU. Ihre Deutung und Behandlung, Gynaekologische Orthopaedie. Von Professor Dr. Heinrich Martius, Direktor der Universitaets-Frauenklinik in Goettingen. With 64 illustrations, 179 pages. Verlag von Georg Thieme, Leipzig, 1939.

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